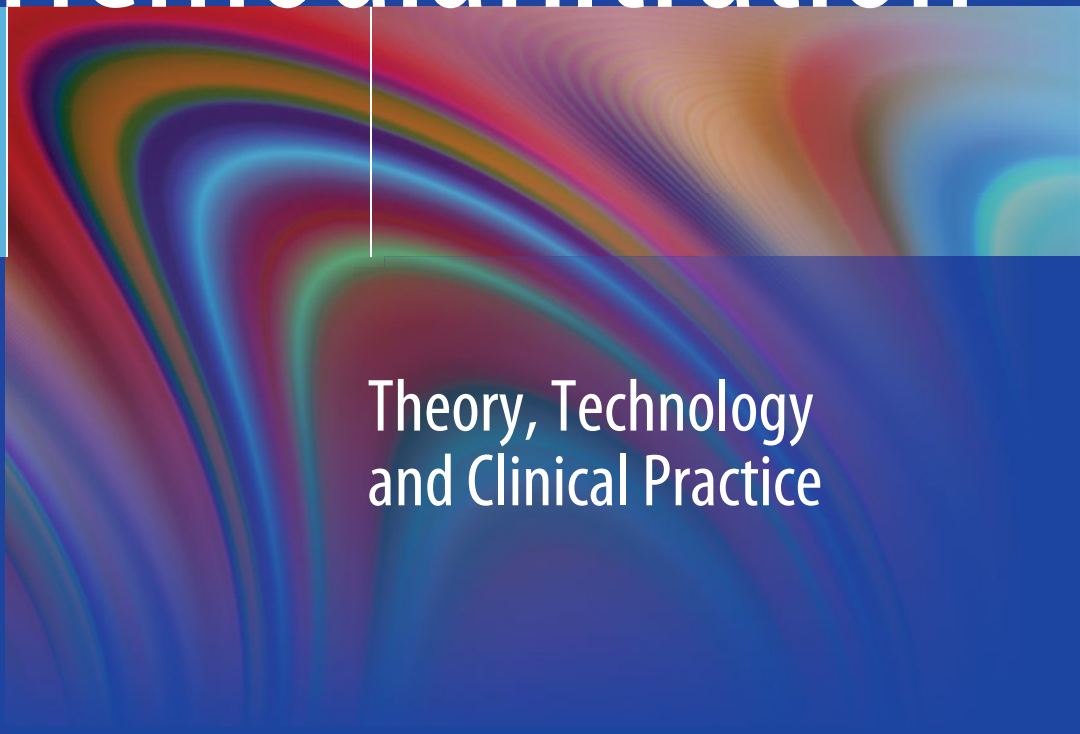
Menso J. Nubé
Muriel P.C. Grooteman
Peter J. Blankestijn
Editors

Hemodiafiltration



Theory, Technology and Clinical Practice

Springer

Hemodiafiltration

Menso J. Nubé • Muriel P.C. Grooteman
Peter J. Blankestijn
Editors

Hemodiafiltration

Theory, Technology and Clinical Practice

Springer

Editors
Menso J. Nubé
VU Medical Center
Amsterdam
The Netherlands

Peter J. Blankestijn
University Medical Center Utrecht
Utrecht
The Netherlands

Muriel P.C. Grooteman
VU Medical Center
Amsterdam
The Netherlands

ISBN 978-3-319-23331-4 ISBN 978-3-319-23332-1 (eBook)
DOI 10.1007/978-3-319-23332-1

Library of Congress Control Number: 2015956130

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

Hemodialysis (HD) has become the standard renal replacement therapy for patients with end-stage kidney disease, with more than two million patients now treated worldwide. However, despite prominent technological improvements over the last decades, the overall 5-year survival for HD patients remains less than that for some of the more common solid organ malignancies, such as colon cancer.

HD is an effective treatment for removing small water-soluble solutes, such as urea by diffusion, but simply increasing urea clearance has not been shown to improve survival. Standard HD with low-flux membranes is not effective in clearing larger middle molecules, such as beta-2-microglobulin, which then accumulates over time, leading to dialysis amyloid deposition. To improve the clearance of these larger uremic toxins, large pore dialyzer membranes (high-flux) were developed, but trials comparing high-flux HD with low-flux HD did not show improved patient survival. The clearance of these larger molecules is much more efficient using convection rather than diffusion, and this led to the introduction of hemodiafiltration (HDF) which provides both efficient diffusive and convective clearances of water-soluble substances.

Technological developments in dialysis machines and water treatment systems have made it possible to treat a significant number of patients with HDF and to analyze various clinical outcome parameters, including overall and cardiovascular mortality. After several observational studies in the past, more recently, three large randomized clinical trials and five meta-analyses have been published. Altogether, results suggest that online postdilution HDF is at least as safe and useful as HD and considerably better when high volumes are applied.

As online HDF has become an established treatment nowadays, and comprehensive information on a diversity of clinical and scientific aspects is available, the time has come to collect and structure this information in a textbook for professionals interested in and/or working with patients with end stage kidney disease. This handbook on hemodiafiltration is divided into five parts. While Part I includes technical and essential aspects of convective techniques, water treatment systems, quality control, and safety requirements (Chaps. 2, 3, and 4), Part II deals with hemodiafiltration equipment. In this part, several machines that can be used for hemodiafiltration

are described, with their general and specific features. The manufacturers are listed in an alphabetic order (Chaps. 5, 6, 7, 8, 9, and 10).

In Part III, the effects of HDF treatment on various biomarkers, such as electrolytes and mineral metabolism, anemia control, inflammation and oxidative stress, uremic toxins, and effects on platelets and coagulation are described (Chaps. 11, 12, 13, 14, and 15). In Part IV, the results of recent large RCTs and meta-analyses on HDF treatment are extensively described and discussed. In addition, in this part attention is paid to the possible mechanisms behind the beneficial effect of high volume HDF on clinical outcome and also to some possible side effects of HDF treatment. Finally, this part also deals with the beneficial effects of HDF on growth in children and nutrition and effects of more intensified HDF strategies (Chaps. 16, 17, 18, 19, 20, 21, and 22). Practical issues, such as how to achieve high volume HDF and how to adapt medication when large convection volumes are applied, are discussed in Part V (Chaps. 23 and 24). Finally, in Part VI the current status of HDF is discussed (Chap. 25). As such, we hope that this handbook on hemodialfiltration has the potential to be of great and global relevance for professionals, the health regulatory authorities and insurance companies, the dialysis industries, and last but not least for the two million or so patients for whom dialysis therapy is a life-saving treatment.

Amsterdam, The Netherlands — Menso J. Nubé
Amsterdam, The Netherlands — Muriel P.C. Grooteman
Utrecht, The Netherlands — Peter J. Blankestijn

Contents

Contributors

Claudia Barth Department of Medical Scientific Affairs, B. Braun Avitum AG, Melsungen, Germany

Peter J. Blankestijn, MD Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands

Michiel L. Bots Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

Björn Bröker Department of Research & Development, B. Braun Avitum AG, Melsungen, Germany

Bernard Canaud, PhD Emeritus Professor of Nephrology, Center of Excellence Medical, Fresenius Medical Care Deutschland GmbH, Bad Homburg v.d.H., Germany

University of Montpellier, School of Medicine, Montpellier, France

Isabelle Chapdelaine, MD Department of Nephrology, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada

Andrew Davenport, MD UCL Centre for Nephrology, Royal Free Hospital, London, UK

Lucia Del Vecchio, MD Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy

Anders Felding, MScEE Technical Services, System Support, Gambro Lundia AB, a subsidiary of Baxter International, Inc., Lund, Sweden

Andrea Fiorenzi, MBA Equipment Operations, Bellco Srl, Mirandola, Italy

Michel Fischbach, PhD Chef de Service Pédiarie 1, CHU Hautepierre, Strasbourg, France

Denis Fouque, MD, PhD Department of Nephrology Nutrition Dialysis, Centre Hospitalier Lyon Sud, Pierre Bénite, France

Emanuele Gatti Department of Health Sciences and Biomedicine, Danube University Krems, Krems, Austria

Griet L.R.L. Glorieux, MSc, PhD Nephrology Division, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium

Muriel P.C. Grooteman, MD, PhD Department of Nephrology, VU University Medical Center, Amsterdam, The Netherlands

Marta Arias-Guillén, MD Department of Nephrology, Hospital Clinic, Barcelona, Catalonia, Spain

Marten Kelm, MBA Department of Medical Scientific Affairs, B. Braun Avitum AG, Melsungen, Germany

Jeroen P. Kooman, MD, PhD Division of Nephrology, Department of Internal Medicine, University Hospital Maastricht, Maastricht, Limburg, The Netherlands

Pascal Kopperschmidt, PhD Department of Global Research & Development, Fresenius Medical Care Deutschland GmbH, Bad Homburg v.d.H., Germany

Detlef H. Krieter, PhD Division of Nephrology, Department of Medicine I, University Hospital Würzburg, Würzburg, Germany

Matteo Lavezzini, PhD Department of Marketing, Nipro Europe N.V., Zaventem, Belgium

Ingrid Ledebo, PhD Director Scientific Support Gambro 1980–2012, Lund, Sweden

Karel M.L. Leunissen, MD, PhD Division of Nephrology, Department of Internal Medicine, University Hospital Maastricht, Maastricht, Limburg, The Netherlands

Francesco Locatelli, MD Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy

Raquel Ojeda López, MD Department of Nephrology, Hospital Clinic, Barcelona, Catalonia, Spain

Francisco Maduell, MD, PhD Department of Nephrology, Hospital Clínic Barcelona, Barcelona, Catalonia, Spain

Lars-Göran Nilsson, BSc Department of Baxter CSO, Renal Therapeutic Area, Gambro Lundia AB, a subsidiary of Baxter International, Inc., Lund, Sweden

Menso J. Nubé, MD, PhD Department of Nephrology, VU University Medical Center, Amsterdam, The Netherlands

Luciano A. Pedrini, MD Department of Nephrology and Dialysis, Nephrocare – Bolognini Hospital, Seriate, Italy

E. Lars Penne, MD, PhD Department of Internal Medicine, Medical Center Alkmaar, Alkmaar, The Netherlands

Uwe Rogalla Department of Sales & Marketing, NIKKISO Europe GmbH, Langenhagen, Lower Saxony, Germany

Claudio Ronco, MD Department of Nephrology Dialysis & Transplantation, International Renal Research Institute (IRRIV), San Bortolo Hospital, Vicenza, Italy

Rukshana Shroff, MD, FRCPCH, PhD Nephrology Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Reiner Spickermann Department of Global Research & Development, Fresenius Medical Care Deutschland GmbH, Bad Homburg v.d.H., Germany

Jan Sternby, PhD Department of R&D, Treatment Systems Research, Gambro Lundia AB, a subsidiary of Baxter International, Inc., Lund, Sweden

Auguste Sturk, PhD Department of Clinical Chemistry, Academic Medical Center, Amsterdam, The Netherlands

James E. Tattersall, MBBS, MD Department of Renal Medicine, Leeds Teaching Hospitals, Leeds, West Yorkshire, UK

Pieter M. ter Wee, MD, PhD Department of Nephrology, VU University Medical Center and ICaR-VU, Amsterdam, The Netherlands

Daisuke Toshigami Technical Department, NIKKISO Europe GmbH, Langenhagen, Lower Saxony, Germany

Daniel J. Touw, PharmD, PhD Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Yoshiro Ueda NIKKISO Europe GmbH, Langenhagen, Lower Saxony, Germany

Frank M. van der Sande, MD, PhD Division of Nephrology, Department of Internal Medicine, Maastricht University Medical Center, Maastricht, Limburg, The Netherlands

Neelke C. van der Weerd, MD, PhD Division of Nephrology, Department of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands

Marc Vervloet, MD, PhD Department of Nephrology, VU University Medical Center, Amsterdam, The Netherlands

Richard A. Ward, PhD Kidney Disease Program, University of Louisville, Louisville, USA

Ariane Zaloszyc, PhD Children Dialysis Unit, University hospital Strasbourg, Strasbourg, France

Anthe S. Zandvliet, PharmD, PhD Department of Clinical Pharmacology and Pharmacy, VU Medical Center, Amsterdam, The Netherlands

Simona Zerbi, MD Nephrology and Dialysis Unit, NephroCare, Bolognini Hospital, Seriate, Italy

Chapter 1
History and Current Status of Online Haemodiafiltration

Bernard Canaud and Ingrid Ledebo

Abstract The genesis of hemodiafiltration (HDF) has followed the general sequence of any new therapy passing through a conceptual phase, a development phase and a long-term evaluation phase with adequate analysis in each step.

In the conceptual phase unmet needs of end stage kidney disease patients treated by hemodialysis were identified, proof of concept was established and the necessary technological development took place.

During the development phase short-term clinical studies demonstrated the safety and efficacy of the online HDF and long-term clinical studies gave evidence of benefits and risks of this new renal replacement modality.

After having satisfied these different steps, any remaining questions and/or uncertainties can be formulated and the future of the therapy can be discussed. In these entire phases one can identify key discoveries and applications that have contributed to major steps forward, often in a new direction.

In this chapter, we have highlighted such events and discussed their importance.

Keywords End stage chronic kidney disease • Renal replacement therapy • Online substitution fluid • Cold sterilization process • Convective dose

Introduction: Why Hemodiafiltration Was Needed?

The development of a new renal replacement therapy corresponds to a need expressed by the nephrology community to correct for shortfalls and/or side effects observed with the use of conventional dialysis. Looking back at the 1970s,

B. Canaud, PhD (✉)
Emeritus Professor of Nephrology, Center of Excellence Medical, Fresenius Medical Care Deutschland GmbH, Else-Kröner-Straße 1, Bad Homburg v.d.H. 61352, Germany

University of Montpellier, School of Medicine, Montpellier, France
e-mail: Bernard.Canaud@fmc-ag.com

I. Ledebo, PhD
Director Scientific Support Gambro 1980–2012, Lund, Sweden

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_1

conventional hemodialysis was performed with low-flux cuprophane membranes, acetate as buffer source and simple pressure devices to control ultrafiltration. The majority of patients were treated in 4–5 h sessions two to three times per week. As a result, efficiency was limited to small water soluble uremic toxins, cardiovascular tolerance was poor and problems with bioincompatibility and dialysis-related pathology started to appear (amyloidosis, accelerated ageing and – atherosclerosis). These factors were pointed out as limitations for long-term sustainability of this supportive therapy. A need for improving hemodialysis treatment both on the short term by improving efficacy and tolerability and on the long term by reducing side-effects was the main focus of clinical research at the time.

The development of a new therapy follows the general sequence of any new therapeutic agent and goes through a conceptual phase, a development phase and a long-term evaluation phase with adequate analysis in each step. In the conceptual phase unmet needs are identified, proof of concept is established and the necessary technological development takes place. During the development phase short-term clinical studies demonstrate the safety and efficacy of the therapy and long-term clinical studies give evidence of benefits and risks. Major milestones achieved in online HDF development over the last four decades has been summarized in Fig. 1.1.

When this is satisfactorily shown any remaining questions and uncertainties are formulated and the future of the therapy can be discussed. In all these phases one can identify key discoveries and applications that have contributed to major steps forward, often in a new direction. For the therapy in focus in this handbook, hemodiafiltration (HDF), we would like to highlight such events and discuss their importance.

Conceptual Phase: How Did We Get There?

Unmet Needs

Renal replacement therapy (RRT) was successfully developed during the 1970s but end stage kidney disease (ESKD) patients were still faced with a high morbidity and mortality risk dominated by cardiovascular diseases [1, 2]. Although the exact

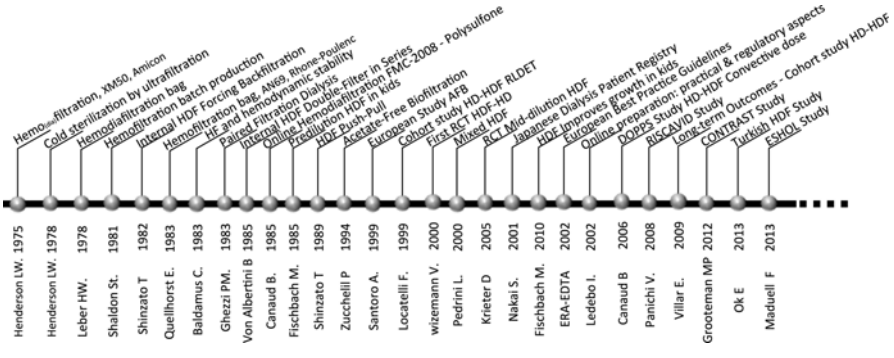


Fig. 1.1 Major milestones achieved in online HDF development over the last four decades

reasons for these shortfalls were not clear, one can acknowledge that they were multifactorial including patient and comorbid risk profile, past history of chronic kidney disease (CKD) and care management before starting dialysis, and RRT efficacy and tolerance.

Considering the pioneering work of Babb [3] and Bergstrom [4, 5], later updated and completed by the Eutox group [6] and others, it becomes clear that uremic toxins comprise a large spectrum of compounds characterized by molecular weights, chemical characteristics, kinetics, protein and tissue binding capacities that extends far beyond that of urea. Focusing on the 'middle and larger molecule' substances it is also obvious that these compounds can only be cleared by means of large pore size membranes and the addition of a driving force such as convection to solute fluxes.

Proof of Concept

In 1975 Henderson et al. using a synthetic ultrafiltration membrane (XM50, Amicon, USA), reported the first clinical application of hemofiltration (HF), although at the time referred to as "hemodiafiltration" [7, 8], see Fig. 1.2. The driving force for this new therapy was the desire to remove "middle molecules", i.e. uremic solutes that were putatively held responsible for some pathophysiologic manifestations of uremia and which could not be cleared in conventional low-flux HD because of their size. Henderson could show that by using pure convective therapy (HF) it was possible to extend the blood purification to include a wide range of large solutes, normally removed by the kidneys. The clinical study also showed that the patients tolerated the HF sessions much better than their regular HD. Fluid removal to reach dry weight was better achieved without symptoms [9, 10]. Correction of hypertension and a high degree of clinical wellbeing was noted among the patients although acetate was used as main buffer [11]. These results led to great expectations from the nephrology community. HF was perceived as a superior dialysis therapy and several groups started clinical trials.

In Europe, Quellhorst pioneered a large HF program using a new high-flux membrane (AN69, Rhone-Poulenc) and conducted controlled crossover studies on patients treated with HD and HF [12, 13]. He and others could show significant improvement of vascular stability and reduced incidence of symptomatic hypotension when patients were treated with HF [14, 15]. These results were presented in the late 1970s, at a time when the hopes of identifying the "middle molecules" were dwindling [16, 17]. HF was still considered an attractive therapy, more because of the improved hemodynamic stability than because of the capacity to remove large solutes. In 1981, Shaldon predicted: "In at least 20–30 % of patients, progress from classical diffusion dialysis will benefit the patient and at the same time improve cost-effectiveness by shortening treatment time, reducing staff requirement and offer better rehabilitation prospects" [18].

During the 1980s, based on urea kinetic modeling (UKM), Gotch and Sargent [19, 20] introduced the concept of dialysis quantification and established Kt/V as the dialysis dose index. Urea was used in this approach as an indicator of dialysis

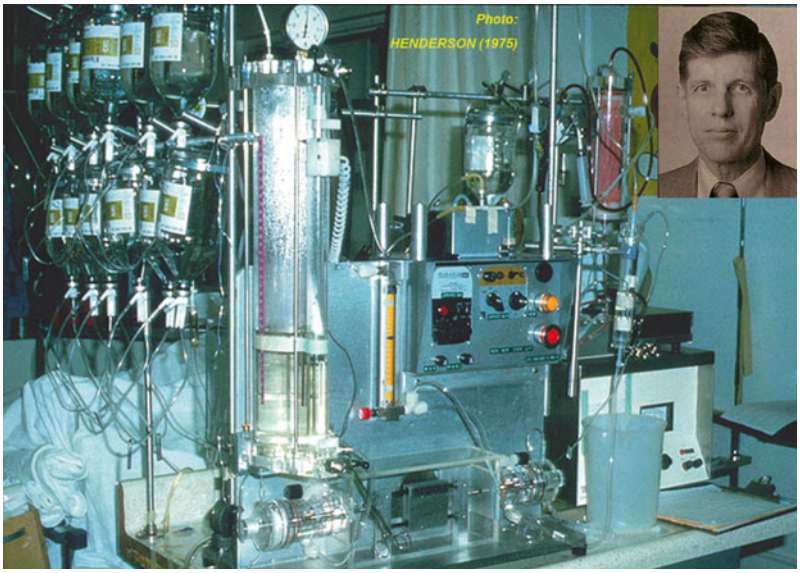


Fig. 1.2 LW Henderson and the first hemo(dia)filtration machine (Reprinted from Henderson et al. [7]. With permission from Elsevier)

efficacy, protein catabolic rate and dietary protein intake, and a surrogate of uremic toxins derived from protein metabolism [21]. Dialysis dose (Kt/V) became a new driving force and focus in the dialysis world for dialysis research and prescription [22]. With the prospect of reducing treatment times and optimizing performances all means were used to enhance the removal of urea. The determinants of diffusive transport – blood flow rate, dialysis fluid flow rate, surface area and permeability properties of the dialysis membrane (KoA) – were all adjusted upwards [23–25]. This meant that HF, which only applies convection and thus provides the same clearance for urea as for larger solutes, was no longer interesting with the ultrafiltration volumes used at the time (20–25 L/session) [26, 27]. However, there were still some pioneering groups in research-oriented hospitals who had experienced the clinical benefits of HF therapy and explored larger ultrafiltration volume to match performances with new standards [28].

During the late 1970s and early 1980s the dialysis industry thrived thanks to the growing number of ESKD patients. Ambitious development projects were started in collaboration with academia and resulted in new membranes and technical innovations that were applied in experimental therapies. One such innovative therapy was the combination of HD and HF, sometimes referred to as "simultaneous HF/HD" and later renamed hemodiafiltration. The entrepreneur group in Giessen, having worked with both HD and HF, felt that each therapy had something to offer [29]. Their goal was to achieve enhanced clearance for small as well as large solutes while maintaining good hemodynamic stability. By combining regular high-flux hemodialysis and forced ultrafiltration with substitution fluid provided in sterilized bags, this group opened a new therapeutic avenue named hemodiafiltration [30, 31].

Technological Development

HDF is technically complex to perform because it requires components needed for both HD and HF [32]. The membrane in the filter should have good diffusive properties, high hydraulic permeability for easy ultrafiltration and generous sieving profile to allow passage of solutes up to the size of albumin. Because the fluid is used for both diffusion and convection, it must meet the corresponding quality requirement, i.e. the dialysis fluid should be at least ultrapure and the substitution fluid be sterile and non-pyrogenic. The fluid composition should be individualized within physiological limits. Access to fluid must not be a limiting factor, which makes on-line preparation integrated with the treatment the only option. This places special hygienic and regulatory demands on the hardware, in addition to accurate volume control and all other functions in modern dialysis equipment.

Technical limitations, mainly regarding membrane permeability and fluid composition and volume, have been the major determinants of the development of HDF therapy during the course of the 35 years it has been applied. The membranes used in the early days were suited for diffusive or convective transport respectively but have been gradually developed and optimized for HDF. Modern membranes combine high diffusive and hydraulic permeability with generous but controlled sieving of solutes. To achieve these characteristics membranes are today made from various synthetic polymers, which can be combined to provide optimal biocompatibility as well as the desired performance.

The fluids have also undergone major changes. In the first HDF trials and for many years the buffer source was acetate in the dialysis fluid, as in HD, and lactate in the substitution fluid provided in autoclaved bags, as in HF. When bicarbonate was introduced in the dialysis fluid, it still took many years until it was included in the substitution fluid. Based on cold sterilization, as described earlier by Henderson [33], Canaud et al. introduced and evaluated for the first time in clinic on-line HDF with bicarbonate using a using a modified HD machine with fluid balancing chambers to control ultrafiltration [34]. After this pilot trial, the feasibility of on-line fluid preparation was recognized and the advantages became apparent. On-line preparation of the sterile fluid used for substitution meant not only that bicarbonate could be used and the electrolyte composition could be individualized. It also made it possible to increase the dose of therapy by exchanging larger fluid volumes, which for practical and economical reasons had been restricted to small research studies when fluid in autoclaved bags were used. Different substitution modalities have been developed to overcome patient barriers and/or to achieve targeted efficacy of the method in peculiar conditions (pre-dilution, mid-dilution and mixed-dilution) [35–38]. It was not until on-line fluid preparation became widely accepted, which with some exceptions occurred in the new millennium, that the limitations imposed by fluid issues were resolved [39–41].

Although described above as a technical limitation the general introduction of on-line fluid preparation should probably be viewed as a regulatory limitation [42]. The ultrafilters required for stepwise removal of bacteria and pyrogens from dialysis fluid were commercially available already in the mid-1980s and prototype systems

for on-line preparation of large volumes of sterile, non-pyrogenic fluid were originally used for HF. However, sterilization by on-line preparation is still not recognized by the Pharmacopoeia and therefore not considered by regulatory authorities, so the approval of dialysis machines with on-line capacity met with serious resistance [43, 44].

In some countries, nephrologists managed to convince authorities to approve on-line HF and HDF, but only with cumbersome safety measures attached to the application, which increased labor and cost [45, 46]. Other countries lacked regulations and practicing nephrologists hesitated to use the therapy. Alternative and/or hybrid therapies have been developed to bypass those regulatory measures and/or to explore additional benefits such as acetate-free biofiltration (AFB) and paired filtration dialysis (PFD) or hemodiafiltration with endogenous reinfusion of substitution fluid after regeneration on resin (HFR) [47–50]. Still, the accumulated European experience on the safety of performing on-line HDF and the potential of the promising data from patients treated with on-line HDF finally broke the barrier and during the new millennium on-line HDF is the only form of the therapy considered [51]. An international guideline covering practical and safety aspects of on-line fluid preparation is now widely approved as standard [52].

While waiting for authorities to approve on-line fluid preparation some groups, mainly in Japan and the US where on-line equipment was not commercially available, developed their own systems for performing diffusion and convection at the same time, without using external fluid for substitution [53–56]. They designed systems that increased ultrafiltration by various pressure manipulations and relied on backfiltration of dialysis fluid to compensate for excess ultrafiltration. This can increase the convective transport compared to HD but not to the extent of optimally prescribed on-line HDF. In addition, the fluid quality may be a problem.

Representing the best of both extracorporeal therapies (HD and HF), hemodiafiltration (HDF) has attracted much interest throughout the western world, i.e. Europe, Japan and the USA, from the early 1980s and it still does, although the therapeutic application and the questions asked have undergone major changes [57]. Considering these changes in the development of the therapy, clinical results from different time periods reflect what could be achieved with the products available at that time, and comparison with modern therapy should be avoided [58].

Clinical Implementation: What Are the Results?

Safety

Online preparation of substitution solution by cold sterilization process from fresh dialysis fluid is a fundamental prerequisite for delivering high-volume HDF and HF modalities. The potential of bacterial-derived products (endotoxin, peptidoglycans, bacterial DNA) entering the bloodstream in case of cold sterilization failure or inadequate disinfection of HDF machine is an important consideration. By applying

strict hygienic rules of disinfection to the online HDF machine, stringent microbial monitoring and periodical replacement of sterilizing ultrafilters, any risk may be virtually abolished. Online blood purification modalities necessitate the use of ultrapure water and certified machines, and the compliance to strict hygienic rules that have been detailed elsewhere [59]. For further reading, see Chap. 3. Several studies have confirmed the safety of the online HDF provided the adequate HDF machines are used and the best clinical practices are applied [60, 61]. The CONTRAST study confirmed in 10 centers over more than 20,000 HDF sessions the reliability and safety of the method [62]. As good clinical practice, it is advisable to monitor clinical symptomatology of HDF treated patients and to ensure measurement of blood sensitive CRP on a monthly basis [63].

HDF Versus HD in Short and Mid-term Studies

During the 1980s the dialysis industry was influenced by the interest in convective therapies and introduced a number of associated technological innovations. New membranes with increased hydraulic permeability, so called high-flux membranes, were made from synthetic polymers and showed improved biocompatibility when exposed to blood. Fluid removal during dialysis was simplified and made more accurate by the incorporation of ultrafiltration control systems in the dialysis equipment. New mixing devices facilitated the inclusion of bicarbonate in the dialysis fluid and acetate was gradually replaced as buffer source.

Although the development of these innovations was triggered mainly by the widespread interest in HF and HDF, they could all be used for HD. Performing HD with high-flux membranes, ultrafiltration control and bicarbonate changed the therapy significantly. The high-flux membrane allowed for increased ultrafiltration, which did not cause excess fluid removal because of the volume was controlled. By means of ultrafiltration controller devices in the HD machine, the excess ultrafiltration was compensated by backfiltration of dialysis fluid. This provided convective clearance, because the membrane was open and because the ultrafiltration was increased [64, 65]. The presence of bicarbonate, and even more so the absence of acetate, enhanced the hemodynamic stability and improved dialysis symptomatology [66, 67]. When high-flux HD was compared with the form of HDF used at the time, so called classical HDF with 9–10 L substitution fluid in bags, which provided around 10–12 L of convective volume, the difference in clearance and symptomatology could not always be detected [68, 69].

When the 1980s changed into the 1990s, urea kinetic monitoring still controlled the prescription of dialysis. Classical HDF provided similar or only slightly higher urea clearance than high-flux dialysis, but was considered more cumbersome to perform and was definitely more expensive, so unless favored by reimbursement it was of little interest to the urea-believers [70, 71]. However, at this time a large retention molecule, β_2-microglobulin (β_2m), appeared on the scene, calling for convective removal [72–74]. Problems with β_2m retention were taken

seriously, especially in Europe and Japan, where more effective and more biocompatible convective therapies were again discussed [75–78]. Both HF and HDF were tested in clinical studies using on-line equipment and large convection volumes [79–84]. Towards the end of the 1990s the flaws of urea kinetic modeling and its consequence, reduced treatment times and poor outcome, became apparent to the dialysis community and studies were designed to test new therapeutic alternatives [85, 86].

In 2002 the HEMO study could not show any difference in survival between patients treated with either low or high urea dose or low-flux or high-flux membranes. A subgroup analysis showed improved survival in long-term dialysis patients treated with high-flux filters and the HEMO investigators made the reservation that "the higher β_2m clearances achievable with HDF might improve outcomes" [87].

HDF in Long-Term Studies: Patient Outcome

The ultimate benefits of HDF/HF therapies in terms of "hard clinical endpoint" such as reduction of β2-M-amyloidosis risk, improved survival and reduced hospitalization that were suggested by retrospective studies have been confirmed by recent prospective randomized controlled trials [88–91]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) first suggested that patients being treated with high-efficiency HDF (15–25 L/session) had a 35 % lower mortality than those treated with low-flux hemodialysis; comparison with high-flux hemodialysis and low-efficiency HDF (<15 L/session), however, was not significantly different [92]. Two recent prospective randomized trials (CONTRAST and Turkish HDF study) failed to show beneficial effects on mortality (all-cause or CV mortality) as primary endpoint. Interestingly, both studies showed, in post-hoc analysis, beneficial effects on all-cause mortality when patients were stratified and allocated to high ultrafiltration volume (>20 L/session), i.e. to high convective dose [93, 94]. The importance of best clinical practices and weakness of these studies was identified since 50–66 % of patients enrolled did not achieve the targeted ultrafiltration volume [95]. The most recent randomized controlled trial, the Catalonian ESHOL study, complying with best clinical practices and achieving targeted ultrafiltration volume in 90 % of patients proved that mortality was reduced by 30 % (all-cause and CV cause) in high-volume HDF treated patients. In addition, the Catalonian study found a reduction of hypotensive episodes (28 %), stroke (61 %) and infection (55 %) [96]. For further reading, see Chap. 16.

Convective Dose Concept

The burning question in HDF today concerns the effective convection volume, i.e. the total undiluted ultrafiltration volume [97–99]. How large should it be to make a difference and how can we best obtain it? To answer this question, a group of

Dutch nephrologists designed the CONTRAST study aiming for 24 L of ultrafiltration, i.e. convection volume, per treatment but only achieved an average of 20.7 L [95, 100]. *Post hoc* analysis showed that the tertiles of patients treated with the highest convection volume, >21.95 L, had significantly improved survival [83]. In parallel a similar study was conducted in Turkey, the Turkish study compared on-line HDF with high-flux HD, aimed for 15 L of infusion solution and achieved an average of 17.2 L [94]. The result was similar to CONTRAST in that no difference in survival could be shown for the total population, but again a *post hoc* analysis of HDF patients treated with the highest convection volume, >21 L (17.4 L substitution + 3.5 L weight loss), had significantly improved survival. The secondary result from these two large, randomized, controlled studies was confirmed by the ESHOL study, which in the primary analysis showed that all patients treated with HDF with convection volumes exceeding 22.9 L per session had significantly improved survival compared with patients on high-flux HD [86]. Further information on the pitfalls and reliability of RCTs and meta-analyses on this subject is provided in Chap. 16.

Remaining or Unsolved Questions Related to Online HDF: Where Are We Today?

Online hemodiafiltration is no longer an experimental treatment, it is a mature renal replacement therapy, used daily to sustain life of more than 160,000 ESKD patients worldwide including 80,000 in the EMEA region [101]. This is presented in Fig. 1.3. Online HDF represents the most advanced treatment modality for end stage kidney disease patients [102]. Considering results of recent RCTs, the time has now come for worldwide, including USA, acceptance of hemodiafiltration as the means to improve ESKD patient outcomes [103].

The use of highly permeable membranes submitted to high transmembrane pressure regime may lead to increased albumin loss, although improvement of membrane manufacturing technology has reduced the sieving coefficient of albumin and minimized losses [57]. For more porous or higher cut-off membranes that do leak albumin, HDF modality exposes the patient to risk significant albumin loss and may not be a good option. Nevertheless, clinical and biologic consequences of albumin loss and hypoalbuminemia must be balanced with the putative beneficial effect of increased removal of uremic toxin-bound substances.

Enhanced loss of nutrients is a theoretical risk associated with all modalities using high-flux membranes and enhanced convective fluxes. Soluble vitamins, trace elements, amino acids, small peptides, and proteins may be lost during high-flux treatments. The total amount of nutrients lost per session is, however, sufficiently low to be easily compensated for by adequate oral intake [104].

Electrolyte balance depends strongly on patient anthropometric characteristics, electrolyte concentrations and convective volume achieved during HDF sessions. Electrolyte prescription (Na, K, HCO3, Ca, Mg) needs to be customized to patient

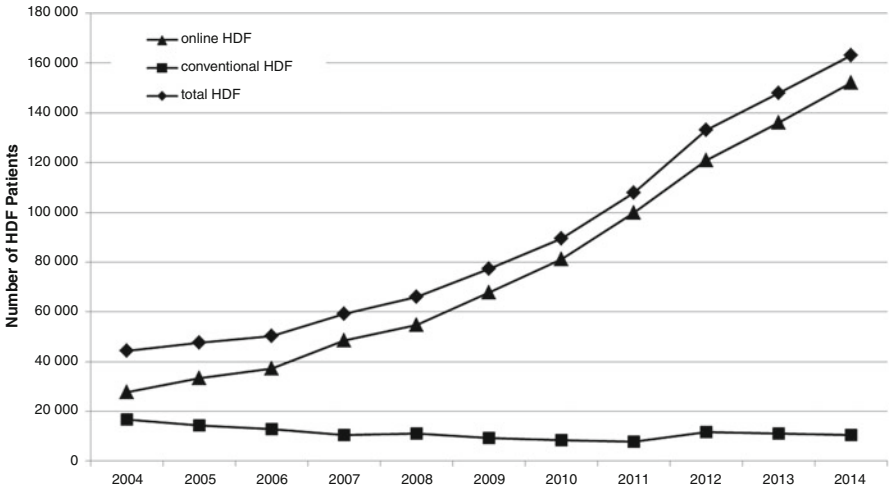


Fig. 1.3 Development of HDF patients from 2004 to 2014 (Based on data from Ref. [103])

metabolic needs and convective volume. Higher ultrafiltration volumes will need to reassess electrolyte mass balance and reset prescription accordingly, since all present reported studies have been performed with restricted ultrafiltration volume (<30 L/session in post-dilution HDF). For further reading, see Chap. 11.

Future Development of Online HDF

Modern online HDF equipment provides a unique technical platform that may be used to facilitate the implementation of new dialysis options (nocturnal HDF, daily HDF) or to revitilize home or self-care renal replacement therapies with automated functions such as auto-priming, rinsing or flushing. With liberal access to sterile apyrogenic fluid new applications can be developed without cost concern.

Conclusions

Online hemodiafiltration can today be considered a mature renal replacement therapy, being used daily to sustain life of more than 80,000 ESKD patients in Europe (18 % of all RRTs). By combining diffusive and convective clearances, online HDF offers the most efficient solute removal capacity over the widest molecular weight spectum of uremic toxins. With high-flux synthetic membrane and ultrapure dialysis fluid, online HDF constitutes the most hemocompatible renal replacement therapy. Safety and efficacy have been proven in numerous short and mid-term clinical studies. Recent randomized controlled clinical trials tend to accredit the superiority of online HDF over contemporary HD, i.e. high-flux HD, to the adequate convective

dose (or convective volume) being delivered. Further clinical trials should establish the optimal convective dose in different clinical settings (patient characteristics and/or ethnicity, substitution modalities) and to establish the cost-effectiveness of HDF compared to contemporary HD.

Teaching Points

- The genesis of hemodiafiltration (HDF) has followed the general sequence of any new therapy passing through a conceptual phase, a development phase and a long-term evaluation phase with adequate analysis in each step.
- In the conceptual phase:
  - Unmet needs of end stage kidney disease patients treated by hemodialysis were identified (high morbidity and mortality risk, retention of uremic toxins in the middle molecular weight range)
  - Proof of concept was established in 1975 (middle molecule removal by hemofiltration)
  - The necessary technological development took place (e.g. combination of hemodialysis with hemofiltration, improvement of dialyzer membranes, online preparation of substitution fluids).
- During the development phase:
  - Short-term clinical studies demonstrated the safety and efficacy of the online HDF.
  - The ultimate benefits of HDF/HF therapies in terms of 'hard clinical endpoint' (e.g. improved survival and reduced hospitalization) as suggested by retrospective studies have been confirmed by randomized controlled trials
- Finally, remaining questions and/or uncertainties can be formulated (e.g. the most effective convection volume, the consequences of loss of albumin and micro-nutrients, electrolyte balance).

References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med. 1974;290(13):697–701.
2. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol. 1998;9(12 Suppl):S16–23.
3. Babb AL, Ahmad S, Bergström J, Scribner BH. The middle molecule hypothesis in perspective. Am J Kidney Dis. 1981;1(1):46–50.
4. Bergström J, Fürst P. Uremic toxins. Kidney Int Suppl. 1978;8:S9–12.
5. Asaba H, Fürst P, Oulés R, Yahiel V, Zimmerman L, Bergström J. The effect of hemodialysis on endogenous middle molecules in uremic patients. Clin Nephrol. 1979;11(5):257–66.

6. Vanholder R, Baurmeister U, Brunet P, Cohen G, Glorieux G, Jankowski J, European Uremic Toxin Work Group. A bench to bedside view of uremic toxins. J Am Soc Nephrol. 2008;19(5): 863–70.
7. Henderson LW, Colton CK, Ford CA. Kinetics of hemodiafiltration II. Clinical characterization of a new blood cleansing modality. J Lab Clin Med. 1975;85(3):372–91.
8. Henderson LW, Silverstein ME, Ford CA, Lysaght MJ. Clinical response to maintenance hemodiafiltration. Kidney Int Suppl. 1975;2:58–63.
9. Baldamus CA, Ernst W, Lysaght MJ, Shaldon S, Koch KM. Hemodynamics in hemofiltration. Int J Artif Organs. 1983;6(1):27–31.
10. Baldamus CA, Shaldon S, Koch KM. Cardiovascular stability in hemodialysis and hemofiltration. In: Cambi V, editor. 'Short Dialysis'. Topics in renal medicine, vol. 3. Boston: Martinus Nijhoff Publishing; 1987. p. 321–64. Chap 14.
11. Schünemann B, Girndt J, Quellhorst E. Hemofiltration as a treatment for "dialysis-resistant" hypertension and hypotensive hyperhydration. J Dial. 1977;1(6):575–83.
12. Quellhorst EA, Schuenemann B, Hildebrand U. Morbidity and mortality in long-term hemofiltration. ASAIO J. 1983;6(4):185–91.
13. Quellhorst EA, Schuenemann B, Mietzsch G. Long-term hemofiltration in "poor risk" patients. ASAIO Trans. 1987;33(3):758–64.
14. Baldamus CA, Quellhorst E. Outcome of long-term hemofiltration. Kidney Int Suppl. 1985;17:S41–6.
15. Quellhorst E, Hildebrand U, Solf A. Long-term morbidity: hemofiltration vs. hemodialysis. Contrib Nephrol. 1995;113:110–9.
16. Fürst P, Zimmerman L, Bergström J. Determination of endogenous middle molecules in normal and uremic body fluids. Clin Nephrol. 1976;3(2):178–88.
17. Nolph KD. Short dialysis, middle molecules, and uremia. Ann Intern Med. 1977;86(1): 93–7.
18. Shaldon S. Progress from hemodialysis. Nephron. 1981;27:2–6.
19. Gotch FA, Sargent JA, Keen M, Lee M. Individualized quantified dialysis therapy of uremia. Proc Clin Dial Transplant Forum. 1974;4:27–35.
20. Gotch FA, Sargent JA, Keen M, Lam M, Prowitt M, Grady M. Clinical results of intermittent dialysis therapy (IDT) guided by ongoing kinetic analysis of urea metabolism. Trans Am Soc Artif Intern Organs. 1976;22:175–88.
21. Gotch FA. Urea guided dialysis therapy. Current clinical results. Dial Transplant. 1976;5:15–8.
22. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526–34.
23. Shaldon S, Florence P, Fontanier P, Polito C, Mion C. Comparison of two strategies for short dialysis using 1m2 and 2m2 surface area dialysers. Proc Eur Dial Transplant Assoc. 1976;12:596–605.
24. Cambi V, Hampl H, Savazzi G, Arisi L, Bignardi L, Garini G, Rossi E, Paeprer P, Kessel M, Migone L. Trans Am Soc Artif Intern Organs. 1978;24:443–7.
25. Trafford JAP, Sharpstone P, Evans R, Ireland R. Evaluation of ultra-short dialysis. Br Med J. 1979;1:518–9.
26. Shaldon S, Beau MC, Deschodt G, Mion C. Mixed hemofiltration (MHF): 18 months experience with ultrashort treatment time. Trans Am Soc Artif Intern Organs. 1981;27:610–2.
27. Quellhorst E, Scheunemann B, Hildebrand U. Hemofiltration: an improved method of treatment for chronic renal failure. Contrib Nephrol. 1985;44:194–211.
28. Canaud B, Araujo A, Sany C, Farrell PC, Garred LJ, Shaldon S, Mion C. A urea kinetic model for haemofiltration. Life Support Syst. 1985;3(1):15–25.
29. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schütterle G. Hemodiafiltration: a new alternative to hemofiltration and conventional hemodialysis. Artif Organs. 1978;2(2):150–3.
30. Wizemann V, Kramer W, Knopp G, Rawer P, Mueller K, Schütterle G. Ultrashort hemodiafiltration: efficiency and hemodynamic tolerance. Clin Nephrol. 1983;19(1):24–30.
31. Wizemann V. Hemodiafiltration: an avenue to shorter dialysis? Contrib Nephrol. 1985;44:49–56.

32. Ledebo I, Blankestijn PJ. Haemodiafiltration-optimal efficiency and safety. NDT Plus. 2010;3(1):8–16.
33. Henderson LW, Beans E. Successful production of sterile pyrogen-free electrolyte solution by ultrafiltration. Kidney Int. 1978;14(5):522–5.
34. Canaud B, N'Guyen QV, Lagarde C, Stec F, Polaschegg HD, Mion C. Clinical evaluation of a multipurpose dialysis system adequate for hemodialysis or for postdilution hemofiltration/hemodiafiltration with on-line preparation of substitution fluid from dialysate. Contrib Nephrol. 1985;46:184–6.
35. Fischbach M, Attal Y, Geisert J. Hemodiafiltration versus hemodialysis in children. Int J Pediatr Nephrol. 1984;5(3):151–4.
36. Krieter DH, Falkenhain S, Chalabi L, Collins G, Lemke HD, Canaud B. Clinical cross-over comparison of mid-dilution hemodiafiltration using a novel dialyzer concept and post-dilution hemodiafiltration. Kidney Int. 2005;67(1):349–56.
37. Santoro A, Conz PA, De Cristofaro V, Acquistapace I, Gaggi R, Ferramosca E, Renaux JL, Rizzioli E, Wratten ML. Mid-dilution: the perfect balance between convection and diffusion. Contrib Nephrol. 2005;149:107–14.
38. Pedrini LA, De Cristofaro V, Pagliari B, Samà F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000;58(5):2155–65.
39. Ledebo I. On-line hemodiafiltration: technique and therapy. Adv Ren Replace Ther. 1999;6(2):195–208.
40. Spalding E, Farrington K. Haemodiafiltration: current status. Nephron Clin Pract. 2003;93(3):c87–96.
41. Canaud B. Online hemodiafiltration. Technical options and best clinical practices. Contrib Nephrol. 2007;158:110–22.
42. Ledebo I. On-line preparation of solutions for dialysis: practical aspects versus safety and regulations. J Am Soc Nephrol. 2002;13 Suppl 1:S78–83.
43. Pirovano D. Regulatory issues for on-line haemodiafiltration. Nephrol Dial Transplant. 1998;13 Suppl 5:21–3.
44. Pirovano D. Regulatory challenges of on-line hemodiafiltration. Contrib Nephrol. 2011;175:69–73.
45. Martin K, Laydet E, Canaud B. Design and technical adjustment of a water treatment system: 15 years of experience. Adv Ren Replace Ther. 2003;10(2):122–32.
46. Canaud B, Bosc JY, Leray H, Morena M, Stec F. Microbiologic purity of dialysate: rationale and technical aspects. Blood Purif. 2000;18(3):200–13.
47. Zucchelli P, Santoro A, Spongano M. Acetate-free biofiltration: acidosis correction and cardiovascular stability. Contrib Nephrol. 1994;108:105–13.
48. Santoro A, Panzetta G, Tessitore N, Atti M, Mancini E, Esteban J, London G, Ara JM, Miguel JL, Neumann KH, Opatrny K, Perez R, Perrone B, Wizemann V, Zucchelli P. A prospective randomised European multicentre study of medium-long run mortality and morbidity comparing acetate-free biofiltration and bicarbonate dialysis. J Nephrol. 1999;12(6):375–82.
49. Ghezzi PM, Frigato G, Fantini GF, Dutto A, Meinero S, Cento G, Marazzi F, D'Andria V, Grivet V. Theoretical model and first clinical results of the paired filtration-dialysis (PFD). Life Support Syst. 1983;1 Suppl 1:271–4.
50. Ghezzi PM. Hemodiafiltration with endogenous reinfusion (HFR): evolution of the method. G Ital Nefrol. 2005;22 Suppl 31:S105–10.
51. European best practice guidelines for haemodialysis (part 1). Section IV: dialysis fluid purity. Nephrol Dial Transplant. 2002;17(Suppl 7):45–61.
52. Quality of dialysis fluid for haemodialysis and related therapies. ISO 11663:2009–2014.
53. Shinzato T, Sezaki R, Usuda M, Maeda K, Ohbayashi S, Toyota T. Infusion-free hemodiafiltration: simultaneous hemofiltration and dialysis with no need for infusion fluid. Artif Organs. 1982;6(4):453–6.
54. Shinzato T, Kobayakawa H, Maeda K. Comparison of various treatment modes in terms of beta 2-microglobulin removal: hemodialysis, hemofiltration, and push/pull HDF. Artif Organs. 1989;13(1):66–70.

55. Miller JH, von Albertini B, Gardner PW, Shinaberger JH. Technical aspects of high-flux hemodiafiltration for adequate short (under 2 hours) treatment. Trans Am Soc Artif Intern Organs. 1984;30:377–81.
56. von Albertini B, Miller JH, Gardner PW, Shinaberger JH. Performance characteristics of the hemoflow F 60 in high-flux hemodiafiltration. Contrib Nephrol. 1985;46:169–73.
57. Blankestijn PJ, Ledebo I, Canaud B. Hemodiafiltration: clinical evidence and remaining questions. Kidney Int. 2010;77(7):581–7.
58. Rabindranath KS, Strippoli GF, Roderick P, Wallace SA, MacLeod AM, Daly C. Comparison of hemodialysis, hemofiltration, and acetate-free biofiltration for ESRD: systematic review. Am J Kidney Dis. 2005;45(3):437–47.
59. Cappelli G, Perrone S, Ciuffreda A. Water quality for on-line haemodiafiltration. Nephrol Dial Transplant. 1998;13 Suppl 5:12–6.
60. Di Felice A, Cappelli G, Facchini F, Tetta C, Cornia F, Aimo G, Lusvarghi E. Ultrafiltration and endotoxin removal from dialysis fluids. Kidney Int Suppl. 1993;41:S201–4.
61. Vaslaki L, Karátson A, Vörös P, Major L, Pethö F, Ladányi E, Weber C, Mitteregger R, Falkenhagen D. Can sterile and pyrogen-free on-line substitution fluid be routinely delivered? A multicentric study on the microbiological safety of on-line haemodiafiltration. Nephrol Dial Transplant. 2000;15 Suppl 1:74–8.
62. Penne EL, Visser L, van den Dorpel MA, van der Weerd NC, Mazairac AH, van Jaarsveld BC, Koopman MG, Vos P, Feith GW, Kremer Hovinga TK, van Hamersvelt HW, Wauters IM, Bots ML, Nubé MJ, Ter Wee PM, Blankestijn PJ, Grooteman MP. Microbiological quality and quality control of purified water and ultrapure dialysis fluids for online hemodiafiltration in routine clinical practice. Kidney Int. 2009;76(6):665–72.
63. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Mazairac AH, Penne EL, Levesque R, ter Wee PM, Nubé MJ, Blankestijn PJ, van den Dorpel MA, CONTRAST Investigators. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. Kidney Int. 2014;86(2):423–32.
64. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58(2):809–17.
65. Lee K, Jeong JH, Mun CH, Lee SR, Yoo KJ, Park YW, Won YS, Min BG. Convection-enhanced high-flux hemodialysis. Artif Organs. 2007;31(8):653–8.
66. Hakim RM, Pontzer MA, Tilton D, Lazarus JM, Gottlieb MN. Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients. Kidney Int. 1985;28(3):535–40.
67. Leunissen KM, Hoorntje SJ, Fiers HA, Dekkers WT, Mulder AW. Acetate versus bicarbonate hemodialysis in critically ill patients. Nephron. 1986;42(2):146–51.
68. Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G, Orlandini G. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. Kidney Int. 1996;50(4):1293–302.
69. Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi E Trapianto. Kidney Int. 1999;55(1):286–93.
70. Dr Devil. Hemodialysis vs. Hemodiafiltration…the future..or another fad? http://ihatedialysis.com/forum/index.php?PHPSESSID=fb10a0c1341ebd2ae0f07af65de46e94&topic=1502.msg18977#msg18977.
71. Blankestijn PJ. Is hemodiafiltration medically superior to hemodialysis? Semin Dial. 2014;27(3):248–9.
72. Gejyo F, Yamada T, Odani S, Nakagawa Y, Arakawa M, Kunitomo T, Kataoka H, Suzuki M, Hirasawa Y, Shirahama T, et al. A new form of amyloid protein associated with chronic hemodialysis was identified as beta 2-microglobulin. Biochem Biophys Res Commun. 1985;129(3):701–6.
73. Gejyo F, Odani S, Yamada T, Honma N, Saito H, Suzuki Y, Nakagawa Y, Kobayashi H, Maruyama Y, Hirasawa Y, et al. Beta 2-microglobulin: a new form of amyloid protein associated with chronic hemodialysis. Kidney Int. 1986;30(3):385–90.

74. Bardin T, Zingraff J, Shirahama T, Noel LH, Droz D, Voisin MC, Drueke T, Dryll A, Skinner M, Cohen AS, et al. Hemodialysis-associated amyloidosis and beta-2 microglobulin. Clinical and immunohistochemical study. Am J Med. 1987;83(3):419–24.
75. Bardin T, Zingraff J, Kuntz D, Drüeke T. Dialysis-related amyloidosis. Nephrol Dial Transplant. 1986;1(3):151–4.
76. Zingraff J, Beyne P, Ureña P, Uzan M, Nguyen Khoa Man, Descamps-Latscha B, Drüeke T. Influence of haemodialysis membranes on beta 2-microglobulin kinetics: in vivo and in vitro studies. Nephrol Dial Transplant. 1988;3(3):284–90.
77. van Ypersele de Strihou C, Jadoul M, Malghem J, Maldague B, Jamart J. Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. The Working Party on Dialysis Amyloidosis. Kidney Int. 1991;39(5):1012–9.
78. Schwalbe S, Holzhauer M, Schaeffer J, Galanski M, Koch KM, Floege J. Beta 2-microglobulin associated amyloidosis: a vanishing complication of long-term hemodialysis? Kidney Int. 1997;52(4):1077–83.
79. Canaud B, Assounga A, Kerr P, Aznar R, Mion C. Failure of a daily haemofiltration programme using a highly permeable membrane to return beta 2-microglobulin concentrations to normal in haemodialysis patients. Nephrol Dial Transplant. 1992;7(9):924–30.
80. Kerr PB, Argilés A, Flavier JL, Canaud B, Mion CM. Comparison of hemodialysis and hemodiafiltration: a long-term longitudinal study. Kidney Int. 1992;41(4):1035–40.
81. Kerr PG, Argiles A, Canaud B, Flavier JL, Mion C. The effects of reprocessing high-flux polysulfone dialyzers with peroxyacetic acid on beta 2-microglobulin removal in hemodiafiltration. Am J Kidney Dis. 1992;19(5):433–8.
82. Lornoy W, Becaus I, Billiouw JM, Sierens L, van Malderen P. Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. Am J Nephrol. 1998;18(2):105–8.
83. Altieri P, Sorba G, Bolasco P, Asproni E, Ledebo I, Cossu M, Ferrara R, Ganadu M, Cadinu F, Serra G, Cabiddu G, Sau G, Casu D, Passaghe M, Bolasco F, Pistis R, Ghisu T, Second Sardinian Multicentre Study. Predilution haemofiltration: the Second Sardinian Multicentre Study: comparisons between haemofiltration and haemodialysis during identical Kt/V and session times in a long-term cross-over study. Nephrol Dial Transplant. 2001;16(6):1207–13.
84. Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. Nephrol Dial Transplant. 2000;15 Suppl 1:43–8.
85. Barth RH. Dialysis by the numbers: the false promise of Kt/V. Semin Nephrol. 1989;2: 207–12.
86. Greene T, Beck GJ, Gassman JJ, Gotch FA, Kusek JW, Levey AS, Levin NW, Schulman G, Eknoyan G. Design and statistical issues of the hemodialysis (HEMO) study. Control Clin Trials. 2000;21(5):502–25.
87. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R, Hemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347(25): 2010–9.
88. Nakai S, Iseki K, Tabei K, Kubo K, Masakane I, Fushimi K, Kikuchi K, Shinzato T, Sanaka T, Akiba T. Outcomes of hemodiafiltration based on Japanese dialysis patient registry. Am J Kidney Dis. 2001;38(4 Suppl 1):S212–6.
89. Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, Rindi P, Donati G, Antonelli A, Panicucci E, Tripepi G, Tetta C, Palla R, RISCAVID Study Group. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. Nephrol Dial Transplant. 2008;23(7):2337–43.
90. Jirka T, Cesare S, Di Benedetto A, Perera Chang M, Ponce P, Richards N, Tetta C, Vaslaky L. Mortality risk for patients receiving hemodiafiltration versus hemodialysis. Kidney Int. 2006;70(8):1524.
91. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009;4(12):1944–53.

92. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, Klassen P, Port FK. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int. 2006;69(11):2087–93.
93. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, den Hoedt CH, van der Tweel I, Lévesque R, Nubé MJ, ter Wee PM, Blankestijn PJ, CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.
94. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, Hur E, Demirci MS, Demirci C, Duman S, Basci A, Adam SM, Isik IO, Zengin M, Suleymanlar G, Yilmaz ME, Ozkahya M, Turkish Online Haemodiafiltration Study. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
95. Penne EL, van der Weerd NC, Bots ML, van den Dorpel MA, Grooteman MP, Lévesque R, Nubé MJ, Ter Wee PM, Blankestijn PJ, CONTRAST investigators. Patient- and treatment-related determinants of convective volume in post-dilution haemodiafiltration in clinical practice. Nephrol Dial Transplant. 2009;24(11):3493–9.
96. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A, ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
97. Tattersall JE, Ward RA, EUDIAL group. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28(3):542–50.
98. Canaud B, Bowry SK. Emerging clinical evidence on online hemodiafiltration: does volume of ultrafiltration matter ? Blood Purif. 2013;35(1–3):55–62.
99. Bowry SK, Canaud B. Achieving high convective volumes in on-line hemodiafiltration. Blood Purif. 2013;35 Suppl 1:23–8.
100. Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, Nubé MJ, van der Tweel I, Ter Wee PM, the CONTRAST study group. Effect of increased convective clearance by on-line hemodiafiltration on all cause and cardiovascular mortality in chronic hemodialysis patients – the Dutch CONvective TRAnsport Study (CONTRAST): rationale and design of a randomised controlled trial [ISRCTN38365125]. Curr Control Trials Cardiovasc Med. 2005;6(1):8.
101. Sichart JM, Moeller S. Utilization of hemodiafiltration as treatment modality in renal replacement therapy for end-stage renal disease patients: a global perspective. Contrib Nephrol. 2011;175:163–9.
102. Golper TA. Technological advances. Semin Dial. 1994;7:323–4.
103. Blankestijn PJ. Has the time now come to more widely accept hemodiafiltration in the United States? J Am Soc Nephrol. 2013;24(3):332–4.
104. Morena M, Cristol JP, Bosc JY, Tetta C, Forret G, Leger CL, Delcourt C, Papoz L, Descomps B, Canaud B. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. Nephrol Dial Transplant. 2002;17(3):422–7.

Part I
Technical Aspects

Chapter 2
Convective Techniques

Luciano A. Pedrini and Simona Zerbi

Abstract A great deal of evidence has now accumulated on the ability of extracorporeal convective therapies to enhance removal of compounds of different molecular weight which are markers or causative agents of severe uremic pathology, such as cardiovascular disease, chronic inflammation, anemia and bone metabolism derangement. A general reduction of the uremic toxicity might be the link with the clinical benefits reported in patients undergoing convective therapies. These benefits may eventually contribute to improving patient survival provided that high convective volume and, thus, high removal of middle-sized compounds is achieved, as suggested by the results of the recently published large trials. Post-dilution hemodiafiltration (HDF), combining diffusion and convection as mechanisms of solute removal, is the most widespread infusion mode in HDF and commonly held as the most efficient in removing middle molecules. Alternative convective and mixed convective-diffusive therapies, exploiting the more common mechanisms of solute transport in different ways, have been developed and proposed in the past years and more recently with the common aim to enhance removal of toxic solutes of different size. An overview of their principles, technical aspects and transport mechanisms on which they are based is provided in this chapter.

Keywords Convective therapies • Convective volume • Hemodiafiltration • Hemodialysis • Hemofiltration • Middle molecules • Mid-dilution hemodiafiltration • Mixed hemodiafiltration • Solute transport • Ultrafiltration

L.A. Pedrini, MD (✉) • S. Zerbi, MD
Department of Nephrology and Dialysis, Nephrocare – Bolognini Hospital, Seriate, Italy
e-mail: axl.pedrini@virgilio.it

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_2

Introduction

A new blood-purification modality based on convection as a mechanism of middle molecular toxins removal was first applied in patients with end stage-renal failure by Henderson and colleagues in 1967 at the University of Pennsylvania [1]. The new technique, coupling diffusion and convection as a transport mechanism, was called 'diafiltration'. The fundamental principles and mathematical relationships of their technique were published some years later [2, 3], but its clinical application was started in Europe by Leber [4], who first proposed the original term 'hemodiafiltration' (HDF) for the new technique, and by Quellhorst, who reported in 1983 promising results of a series of studies in patients over a long time period [5].

Continuous evolution of HDF took place from its birth until the more recent modalities of its application. Introduction of bicarbonate buffer in dialysis fluid and replacement solutions minimized the relevant side-effects caused by the acetate or lactate contained in the original fluids. The development of new synthetic highly biocompatible and permeable membranes with selective cut-off extended the range of removed compounds to small molecular weight proteins and beyond, while minimizing albumin loss. On-line production of indefinite amount of ultrapure dialysate/substitution fluid at low cost replaced the cumbersome and expensive use of fluids in sterile bags. The ultrafiltration (UF) control systems, introduced to control body weight (BW) loss with fluximeters measuring the differential flow between outlet and inlet dialysate compartment, were adapted to optimize and safely modulate the infusion rate (Q_{inf}) through a feedback mechanism controlled by the trans-membrane pressure (TMP). Nowadays, technological progress of dialysis systems grants a high level of efficiency and safety to the convective techniques with the application of advanced feedback devices, operating automatically and easily controlled through a friendly user interface. In the last years, different infusion modalities in HDF have been proposed as alternatives to the traditional post-dilution and pre-dilution modes, combining convection, diffusion and adsorption to a different extent, but with the common aim to improve the operational and clinical feasibility of convective therapies and to achieve maximal solute removal in a wide spectrum of molecular weights.

Water and Solute Transport in Convective Therapies

Ultrafiltration

Ultrafiltration (UF) of plasma water occurs as a consequence of a pressure gradient across the dialyzer membrane modulated by applying a negative pressure in the dialysate compartment of the filter. The driving force for water filtration at every point of the capillary length of the dialyzer is the resultant of the hydraulic pressure inside the fiber (P_B) and in the dialysate compartment (P_D) and the oncotic pressure

exerted by plasma proteins (π), which opposes to filtration. The average pressure gradient across a dialyzer membrane (TMP) may be calculated as:

$$TMP = \left(P_{Bin} + P_{Bout}\right)/2 - \left(P_{Din} + P_{Dout}\right)/2 - \left(\pi_{in} + \pi_{out}\right)/2 \quad (2.1)$$

where the suffix *in* and *out* indicate the inlet and outlet ports of the two dialyzer compartments.

The volumetric water flux (J_f) is a function of TMP according to the equation [6, 7]:

$$J_f / A = L_p * TMP \quad (2.2)$$

where L_p is the hydraulic permeability of the membrane for water, i.e. the water flow rate per unit area of membrane (A) per unit TMP gradient (ml/min/cm^2/mmHg).

Water permeability of a dialyzer membrane is defined in clinical practice with its UF coefficient (K_{UF}, ml/h/mmHg/m^2) according to the equation:

$$K_{UF} = Q_{UF} / TMP / m^2 \quad (2.3)$$

where Q_{UF} is the UF rate.

When referred to the overall membrane surface of a dialyzer K_{UF} becomes $K_{UF}D$, ml/h/mmHg:

$$K_{UF}D = Q_{UF} / TMP \quad (2.4)$$

$K_{UF}D$ corresponds to the slope of the regression equation [6] relating Q_{UF} with TMP and characterizes numerically the hydraulic permeability of that dialyzer, which largely depends on the surface and characteristics of the membrane (mainly the pore radius), and on the dialyzer geometry. A nominal $K_{UF}D$ >40 ml/h/mmHg is a requisite for high-flux dialyzers.

Lower than nominal $K_{UF}D$ values are found in vivo as a consequence of the protein layer formation on the inner face of the membrane (secondary membrane). Loss in hydraulic permeability is negligible and quite constant along low-flux HD sessions conducted at moderate Q_{UF} [8]. Progressive and even substantial reduction in $K_{UF}D$ may be observed during HDF and hemofiltration (HF) sessions when higher Q_{UF} and filtration fraction (FF) are applied, as an effect of the solute and protein polarization on the inner membrane surface and thickening of the secondary membrane [9, 10]. In addition, the colloid osmotic pressure exerted by the concentrated plasma proteins counteracts the filtration pressure [11]. As a consequence, the modern feedback systems are very effective in preventing this risk by adapting Q_{UF} to the actual operating conditions and reducing it automatically whenever TMP rises to dangerous values. Besides the hydraulic permeability properties of the membrane, maximal Q_{UF} level is mainly a function of the blood flow rate (Q_B) permeating the capillaries of the dialyzer. Therefore, high Q_B are preferential for the production of high UF and convective removal and, thus, to achieve high efficiency in the application of convective therapies.

Convection

Convection is the main transport mechanism of middle molecular size solutes in mixed convective-diffusive therapies. Convective solute removal is the result of the bulk movement of the solvent (plasma water) across the membrane driven by the hydrostatic pressure gradient between blood and dialysate compartments. Convective transport is constant over a wide range of molecular weight solutes but decreases as the hydrated molecular size approaches that of the pores of the membrane. In general, the degree to which convection increases total solute removal is proportional to Q_{UF} and to the molecular weight of the solute [12]. The membrane characteristics (electro-chemical properties and structure, pore radius and conformation) also play an important role [13–16]. The ability of a membrane to remove a specific solute from plasma by convection is determined by its sieving properties and expressed mathematically with an index, the sieving coefficient (S_C, dimensionless), unique for that solute and that membrane. Sc, measured in vitro in a defined experimental setting and in the absence of diffusion, is the ratio between the solute concentration detected in the UF (C_{uf}) and its average plasma concentration within the dialyzer [6]:

$$S_c = 2C_{uf} / \left(C_{in} + C_{out}\right) \tag{2.5}$$

According to Eq. 2.5, S_c value is inversely related to the solute molecular weight and varies between 1 for a freely permeable molecule and 0 for a molecule to which the membrane is completely impermeable. However, in a clinical setting, the same events that limit the hydraulic permeability of the membrane and reduce Q_{UF} may also affect removal of middle-molecular solutes by convection. As a consequence of the progressive thickening of the secondary membrane layer the in vivo S_C value (apparent sieving) for molecules such as beta2-microglobulin (β2-m) may results in lower values than those measured in vitro and may even approach zero in post-dilution HF at very high Q_{UF} [17].

Convective transport of a solute (J_C) may be expressed with the mathematical equation which defines its relation with the solute plasma concentration (C) and the rate of fluid transfer across the membrane Q_{UF}, limited by the solute and membrane Sc:

$$J_C = Q_{UF} * C * S_C \tag{2.6}$$

The equation also defines the clearance of the solute when pure convection is applied in HF.

Diffusion

Diffusion is the main transport mechanism of small molecular size solutes also in mixed convective-diffusive therapies. Solute diffusion follows a trans-membrane

concentration gradient between blood and dialysis fluid according to a first-order kinetics and the process is represented mathematically by the Fick's law:

$$J_D / A = -K_o * dc / dx \tag{2.7}$$

where J_D is the rate of solute diffusive flux per unit area of the membrane (A), proportional to the solute concentration gradient (dc/dx), and K_o is the overall mass transfer coefficient (or solute diffusion coefficient), which is a property of the membrane and the solute and characterizes the overall resistance to a definite solute flux across a unit area of that membrane. When referred to the overall surface of a dialyzer, its diffusion coefficient for a specific solute is defined with the expression KoA (i.e. overall mass transfer coefficient *area). According to the Eq. 2.7, diffusive transport is proportional to the surface area of the membrane: progressive increase in dialyzer surface at constant Q_{UF} results in moderate enhancement of the diffusive transport according to a curve that achieves its plateau faster for small molecular solutes. The level of the plateau is a function of the diffusive permeability of the membrane.

Diffusion property of a dialyzer is also influenced by blood and dialysate flow rates (Q_B, Q_D), and the relative role of each factor depends on K_oA, according to the equation by Michaels [18]

$$K_D = \frac{1 - EXP\left[K_oA * \left(Q_B - Q_D\right) / \left(Q_B * Q_D\right)\right]}{1/Q_B - 1/Q_D * EXP\left[K_oA * \left(Q_B - Q_D\right) / \left(Q_B * Q_D\right)\right]} \tag{2.8}$$

where K_D is the diffusive dialyzer clearance. The effect of increasing Q_B up to 500–600 ml/min progressively increases K_D of small solutes to a greater extent than that of middle-high molecular weight solutes, which is scarcely affected by Q_B values beyond 200–250 ml/min [19]. An increase in Q_D from 500 to 800 ml/min results in a small-moderate enhancement of small solute removal by diffusion but not of the larger solutes [20–22].

Interactions Between Diffusion and Convection

Convection and diffusion act simultaneously as solute transport mechanisms in HDF, even if to a different extent according to the molecular weight of the removed solute. However, the overall mass transport is not the sum of the two separate components because of an interaction between them, which is more prominent at the high Q_{UF} of HDF. Their effects cannot be distinguished from each other, but some mathematical models have attempted to quantify their combined effect in term of solute removal. The simplest model is described by the equation [23]:

$$K_{HDF} = K_D + Q_{UF} * T \tag{2.9}$$

where K_{HDF} is the overall (convective + diffusive) clearance, and T is the transmittance coefficient, a parameter which is a function of the flow conditions and membrane properties. An expression for T that is universal for all solutes is:

$$\text{with} Q_{UF} < 70 \text{ml} / \text{min} : K_{HDF} = K_D + 0.46 * Q_{UF} \quad (2.10)$$

$$\text{with} Q_{UF} > 70 \text{ml} / \text{min} : K_{HDF} = K_D + 0.43 * Q_{UF} + 0.00083 Q_{UF}^{\ 2} \quad (2.11)$$

Absorption

Absorption assumes relevance as a removal mechanism particularly in the case of some high-flux membranes carrying electrical charges, such as polyacrilonitrile and polymethyl-metacrilate [24, 25], and may significantly enhance the dialyzer clearance of β2-m and of several cytokines. Polysulfone membranes show minor absorptive capacity and remove middle molecule compounds mainly by convection [26]. Electrochemical interaction between these membranes and certain hydrophobic compounds like peptides and proteins may cause them to adhere on the inner surface of the membrane within the pore structure [27]. Therefore, the open pore structure of high-flux membranes affords more absorptive potential than do low-flux membranes, and synthetic hydrophobic membranes are generally much more absorptive than hydrophilic cellulosic membranes [28]. Albumin coats the membrane immediately after exposure to blood, with the effect to reduce its in vivo permeability. Absorption characteristics of high-flux membranes are more extensively defined in another chapter.

Teaching Points I

- Convection is the main transport mechanism of middle molecular size solutes in mixed convective-diffusive therapies
- Convective solute removal is the result of the movement of plasma water across the membrane, driven by the hydrostatic pressure gradient between blood and dialysate compartments.
- The driving force for water filtration is the resultant of this pressure gradient and the oncotic pressure exerted by plasma proteins, which opposes filtration.
- Diffusion is the main transport mechanism of small molecular size solutes also in mixed convective-diffusive therapies. Solutes follow a transmembrane concentration gradient between blood and dialysis fluid according to a first-order kinetics
- Convection and diffusion act simultaneously as solute transport mechanisms in HDF

Modalities of Convective Therapies

Internal Hemodiafiltration (iHDF)

A certain amount of solute removal by convection may also be obtained during prevalent diffusive treatments when high-flux dialyzers are used. In this case, the TMP gradient established in the proximal part of the dialyzer promotes large water transfer from blood to the dialysate. Water acts as solvent drag and favors removal of middle molecular compounds by convection. Hydraulic pressure on the blood side drops progressively along the fibers, while oncotic pressure increases with plasma protein concentration until, at a certain point of the dialyzer length, the pressure gradient across the membrane reverses its direction and, accordingly, UF ceases and water moves from the dialysate compartment to blood (Fig. 2.1). This mechanism, called 'back-filtration' or 'internal filtration' is the underlying principle of high-flux HD and its effect is an enhancement of small- and middle-molecular solute removal by convection [29]. iHDF works just as a high-flux HD, but it requires the convective dose to be clinically relevant, quantifiable and possibly adjustable by the operator. This technique entails the use of a dedicated dialyzer with geometric characteristic suitable for increasing internal filtration. iHDF improves convective transport by direct filtration and backfiltration without the need of substitution fluid infusion [30]. A user-friendly mathematical model has been designed to quantify the internal filtration/backfiltration flux taking place during the treatment. Flux is predicted on the basis of the machine settings and hematocrit/plasma protein concentration [31, 32].

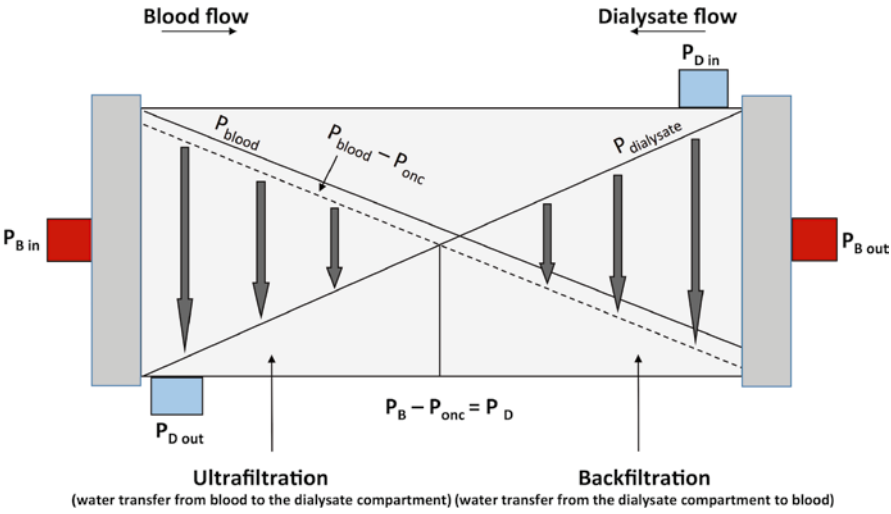


Fig. 2.1 Schematic representation of internal filtration as a convective transport mechanism acting during high-flux HD

Hemofiltration (HF)

This technique realizes pure convective solute transport without solute exchange by diffusion in the absence of dialysate flow and, thus, more closely mimics the glomerular filtration of the human kidney than any other dialysis technique. As a consequence, HF promotes a higher rate of medium- and large molecules removal than low- and high-flux HD but lesser removal of small solutes which are mainly removed by diffusion. Achievement of high convective volume is often difficult in the post-dilution mode of HF, during which rapidly progressive hemoconcentration in the dialyzer and significant loss of hydraulic membrane permeability may occur at very high Q_{UF}. Only the pre-dilution mode may partially obviate these drawbacks of HF by improving flux rheology, membrane permeability and convective removal of all solutes thanks to the increased flow along the dialyzer capillaries. Some clinical benefit of this technique in terms of hemodynamic stability was reported in the past as a consequence of a better vascular reactivity in the absence of vasodilator acetate in dialysis fluid [33, 34], and was variably attributed to the removal of vasoactive destabilizing factors with convection [35, 36], blood cooling after mixing with the substitution fluid [37], or sodium retention and positive sodium balance due to the Donnan effect [38]. These advantages of HF faded when bicarbonate buffer was introduced and temperature and sodium balance were matched with HD and HDF with the modern dialysis systems. Thus, the positive effect of HF on hemodynamic instability remains unexplained. Moreover, more recent observations have reported lower incidence of intradialytic hypotension during on-line HDF than on HF and high-flux HD, see also Chap. 17 [39].

Hemodiafiltration

High Q_{UF} may be obtained in HDF, in the absence of significant back-filtration due to a constantly positive pressure gradient between blood and dialysate along the dialyzer capillary. Solutes with diameter up to that of the membrane pores are dragged across the membrane with the UF flow independently of their molecular size, while transfer of small-molecular toxic compounds from blood to dialysate occurs by diffusion according to a concentration gradient. Combining both removal mechanisms into a single treatment (HDF) is undoubtedly the strategy enabling the high potential of hydraulic and solute permeability of synthetic membranes to be most properly exploited.

Post-dilution HDF

This technique is the most widespread infusion mode in HDF and commonly held as the most efficient in removing middle molecules [12, 19, 40, 41]. Sterile substitution fluid is produced on-line from the dialysate by the more recent HDF systems and is infused after the filter to replace the excess fluid lost by the patient with the

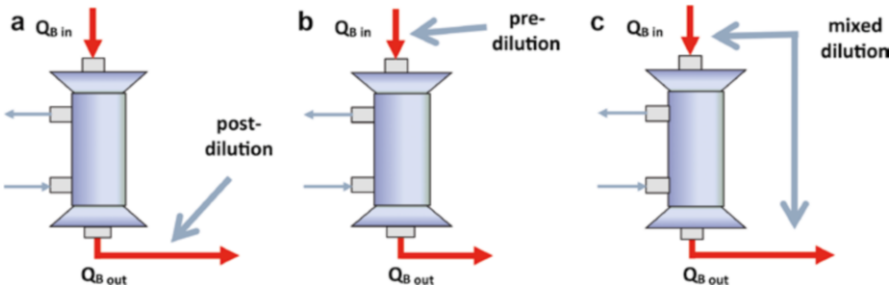


Fig. 2.2 Infusion modalities in HDF. (**a**) post-dilution HDF; (**b**) pre-dilution HDF; (**c**) mixed HDF

high UF (Fig. 2.2a). Up to 5–6 l of UF per hour may be obtained by applying appropriate flux-pressure regimen. Proportional increase in β2-m removal is achievable in post-dilution HDF with increasing Q_{UF} [12, 19] and lower β2-m basal level have been associated with a reduced death risk in dialysis patients [42]. Indeed, observational [43] and prospective randomized trials [44–46] have shown that post-dilution on-line HDF may obtain a substantial reduction of the death risk in dialysis patients, with improved survival of around 30 % compared to low- and high-flux HD, provided that high convective volume is achieved per session (21–23 l).

Thus, clinical application of on-line HDF requires operating conditions to be set in order to achieve this goal and maximally exploit the convective potential of high-flux membranes. At any given blood flow the maximal efficiency in convective removal is obtained at the highest FF [40], but the highest achievable FF value is often unpredictable. When very high Q_{UF} are applied in post-dilution HDF, hemoconcentration increases blood viscosity and resistance to flow inside the fibers, especially when high rates of weight loss are necessary to achieve the dry body weight and when the individual capacity to recruit fluid from the extra-vascular space during dehydration (refilling) is scarce. In these conditions, a critical reduction of the membrane permeability is likely to occur as a consequence of the events described above [9–11] and the relationship between Q_{UF} and TMP, linear up to a certain TMP value (200–300 mmHg for high-flux membranes), becomes curvilinear and progressively increasing TMP is necessary to maintain the programmed filtration, until a plateau is reached [6], beyond which the system becomes unstable [47], increasingly higher TMP gradients fail in the attempt to maintain the planned Q_{UF} and sudden dangerous pressure peaks are likely to result from small changes in blood flow or viscosity, venous pressure, or for clinical reasons, particularly in patients with cardiac failure, diabetes or hemodynamic instability. In such circumstances circuit clotting and residual irreversible reduction in the performance of the dialyzer may be observed. Historically, the limit beyond which the adverse events of high TMP levels and hemoconcentration may occur was set empirically at a plasma water FF of 0.5 [6]. Setting Q_{UF} purely on the basis of the in vitro $K_{UF}D$ may be misleading for several reasons.

The present technology of HDF machines helps to automatically plan a session of post-dilution HDF in order to safely accomplish this task with the use of feedback

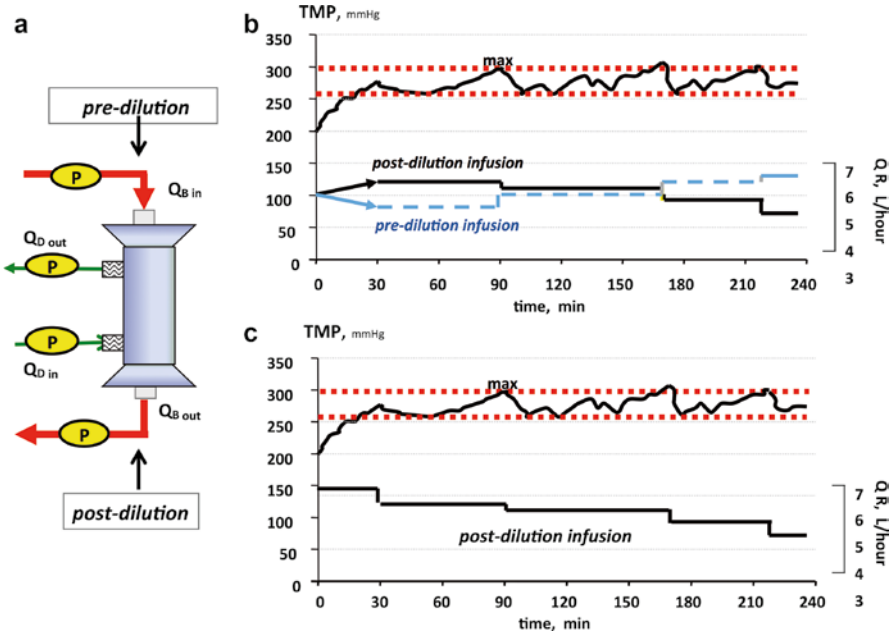


Fig. 2.3 (**a**) Schematic representation of the hardware for mixed HDF implemented on the 5008 Fresenius Therapy system. Instantaneous mean TMP values are calculated from the measures of four pressure probes (P) placed at the inlet and outlet blood and dialysate compartments. Infusion lines are connected at the inlet and outlet lines of the extracorporeal circuit. (**b**) In Mixed dilution HDF, the TMP/UF feedback system maintains TMP values within the maximum safe range by modulating the total infusion and the ratio between post- and pre-dilution infusion. (**c**) In post-dilution HDF, TMP is controlled by modulating the total infusion. The diagrams represent the mechanism by which the TMP/UF feedback works in the two modalities. More details are in the text

devices which sets and maintains the infusion rate under TMP control and reduces it whenever TMP increases beyond its maximum limit as a consequence of the progressive decline of the membrane permeability through the session (Fig. 2.3c).

However, high convective volume may only be achieved by applying high Q_B in order to maximally increase the capillary flow of plasma water available for UF and better preserve the membrane permeability by enhancing the stirring and thinning actions exerted by the blood flow on the protein layer on the blood side of the membrane.

Pre-dilution HDF

This technique may ensure more favorable rheological and hydraulic conditions than the post-dilution mode by better preserving the permeability of the membrane, as the replacement fluid added to blood at the dialyzer inlet prevents excessive hemoconcentration and increases the rate of flow within the capillaries with enhanced shear-rate effect on the secondary protein layer (Fig. 2.2b). This advantage may be offset by the dilution effect of the plasma solute concentrations

available for diffusion and convection, with consequent reduction of the cumulative solute transfer [19, 40, 41, 48]. Accelerated extraction of diffusible small solutes from the intracellular space has been described as an effect of a more favorable transcellular gradient [2, 49], but this mechanism is unable to fully compensate for loss in efficiency. Only a substantial increase of the infusion rate up to a value approximately double with respect to post-dilution HDF may result in similar removal of middle molecular solutes between the two infusion modalities [19]. Clinical application of pre-dilution HDF is limited by the above drawbacks and by the cost related to the increased amount of replacement solution to be prepared from the dialysate. It may be indicated in patients with high hematocrit or hemorrhagic to help in the anticoagulation of the extracorporeal circuit.

Mixed HDF

This technique, in which the replacement fluid is simultaneously infused to a variable ratio at the inlet and outlet port of the dialyzer, was developed in the last decade (Figs. 2.2c and 2.3a). The aim is to overcome limits and risks implicit in the traditional infusion modes in HDF while coupling their advantages [40, 50, 51]. The basic concept is that more favourable rheological and hydraulic conditions than in post-dilution HDF are ensured within the dialyzer by splitting the infusion between pre- and post-filter. An increase in blood flow rate obtained with partial and controlled pre-dilution may better preserve the characteristics of water and solute permeability of the membrane, while avoiding the excessive dilution of the inlet solute concentrations characteristics of the pre-dilution mode. In mixed HDF, a convective volume of up to 40–45 l/session may be attained under the control of an original feedback system device which ensures maximal filtration fraction by favoring the infusion at the post-dilution port (60–70 % of the total infusion). The feedback system maintains TMP within the highest range of safety during the session by splitting small amounts of substitution fluid from the post- to the pre-dilution site whenever TMP rises to its highest safety limit (300–350 mmHg) without reducing the total infusion rate (Fig. 2.3b) [50, 52].

Validation studies have shown that greater β2-m and phosphate removal may be safely obtained in on-line mixed HDF than in post-dilution HDF by ensuring optimal operating conditions of the technique and forcing Q_{UF} to achieve the most efficient convective transport [48, 52–55].

Mixed HDF may be of special advantage in patients with high pre-dialysis hematocrit and an increased risk of filter clotting with post-dilution HDF due to hemoconcentration [56], and more in general in all those patients who cannot achieve the desired convective volume in post-dilution HDF, due to different clinical and technical situations.

Mid-dilution HDF (MD-HDF)

This technique was proposed by Krieter as a step ahead in terms of improved convective solute transport (Fig. 2.4) [57]. It is based on the use of dedicated hemodiafilters which include a unique U-shaped blood capillary bundle and a special

two-port header cap (Olpur™ MD 190 and MD 220, Nephros, New York, USA). Blood flows through the annular region of the fiber bundle, mixes with substitution fluid infused through a middle infusion port placed at the point where blood flow reverses its direction and flows in the reverse direction through the core region of the fiber bundle. Blood and dialysate flow counter-current in the annular region of the capillaries where post-dilution is performed and co-currently in the core, pre-dilution region.

This infusion technique has been claimed to achieve greater efficiency when compared to traditional post-dilution HDF [57]. However, a prospective comparative analysis between on-line mixed HDF and MD-HDF showed that MD-HDF was carrying with it serious membrane permeability impairment when applied as proposed in the original study because considerably high TMP in the post-dilution section of the hemofilter were necessary to achieve the planned UF of about 10 l/h [58]. This problem was overcome by devising a new configuration, called reverse MD-HDF, in which blood inlet and outlet were inverted. In the new setting blood flows through the core region of the fiber bundle, mixes with substitution fluid at the other end, and flows in the reverse direction through the annular region of the fiber bundle [59]. Anyway, safe rheologic and hydraulic conditions in MD-HDF may only be maintained by carrying out treatments with the larger MD 220 hemofilter (2.2 m^2) in reverse MD-HDF configuration [60]. The total solute removal of reverse MD-HDF with the larger MD 220 hemofilter and post-dilution HDF appears to be not different from post-dilution HDF for both small water-soluble and protein-bound compounds [61]. An efficient pressure control system with modulation of the infusion rate according to the operational conditions of the treatments, would be useful to improve safety and performance in the clinical application of this technique.

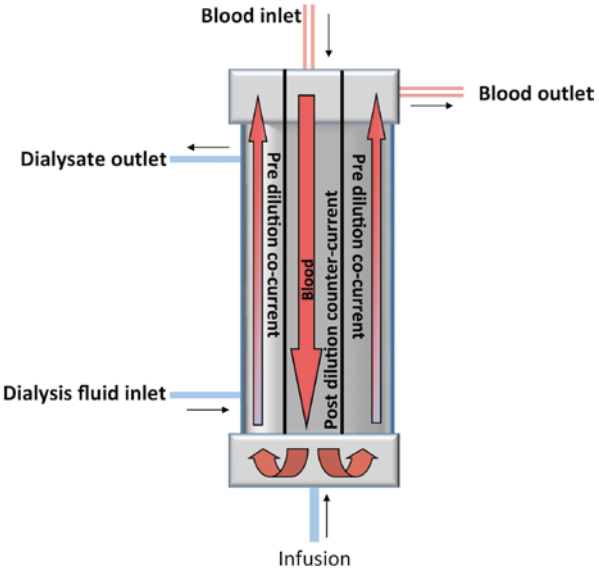


Fig. 2.4 Schematic representation of mid-dilution HDF (MD-HDF)

HDF with Endogenous Reinfusion (HFR) (Fig. 2.5)

This technique was designed to separate the two main transport processes, convection and diffusion, with the use of a two-chamber filter and a sorbent cartridge [62–66]. Isolated plasma UF and solute convection take place through the polyethersulfone high-flux membrane of the first chamber of the dialyzer. The UF produced in the first chamber is 'regenerated' while flowing through a sorbent cartridge and then infused in the second dialyzer chamber as endogenous replacement solution. The diffusion stage occurs in the second chamber through a low-flux polyethersulfone membrane. The sorbent cartridge contains a hydrophobic styrenic resin which has high affinity and adsorbs several uremic toxins and MM, such as β2-m, homocysteine, parathyroid hormone and several cytokines. Electrolytes and small solutes such as urea, creatinin and uric acid are not adsorbed and are managed in the second, diffusive section of the dialyzer [63, 67]. Lower impact on oxidative stress [68] and sparing effect on amino acids loss [69] have been reported in HFR compared to HD and acetate-free biofiltration (AFB), respectively. The recent development of HFR equilibrium, based on the combination of HFR with dialysate sodium and UF profile, has been shown to improve intradialytic hemodynamics [39].

Push/Pull Hemodiafiltration (PP-HDF)

This technique is one of the most widespread modalities used in Japan and South Korea (Fig. 2.6). It's based on a double-cylinder piston pump (push/pull pump) implemented on the effluent dialysate line of the dialysis machine. Based on this alternate pump device, alternate fast cycles of UF (pull) and backfiltration (push) are performed through a high-flux dialyzer [70, 71]. During the UF phase, uremic substances are eliminated both by diffusive and convective transport. During the backfiltration phase, dialysate is forced to the blood side in order to balance the

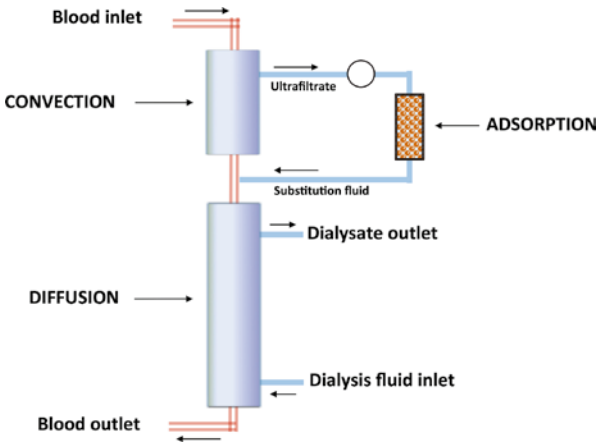


Fig. 2.5 Schematic representation of HDF with endogenous reinfusion (HFR)

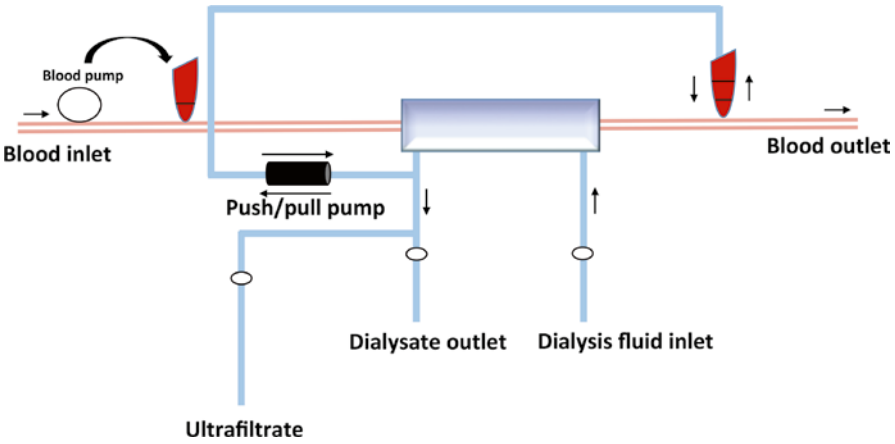


Fig. 2.6 Schematic representation of push/pull hemodiafiltration (PP-HDF)

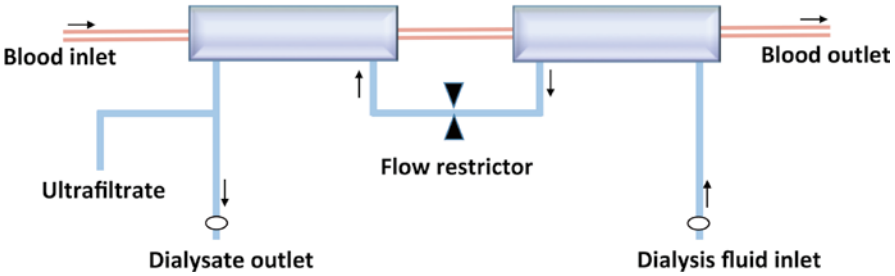


Fig. 2.7 Schematic representation of double high-flux hemodiafiltration (DHF-HDF)

excessive reduction in body fluid developed during the previous UF phase. Body fluid replacement volume is over 120 l during a 4-h treatment. Since the UF and backfiltration times are much shorter in PP-HDF than the time for blood to pass through the dialyzer, blood is concentrated and diluted many times before it leaves the dialyzer. High removal rate of middle molecules and reduction of symptoms of dialysis-related amyloidosis have been reported with this technique [72, 73].

Double High-Flux Hemodiafiltration (DHF-HDF)

This technique was designed in the beginning of 1980s in order to achieve a drastic reduction of treatment time over conventional HD and increase convective transport without the need for ultrapure substitution fluid and consequently dedicated machines. DHF-HDF (Fig. 2.7) consists of two high-flux dialyzers connected in series by blood and dialysate lines [74]. Fluid and solutes are removed in the first dialyzer with a mixed diffusion-convection process, while backfiltration of sterile dialysate takes place in the second dialyzer. An adjustable flow-restrictor is placed

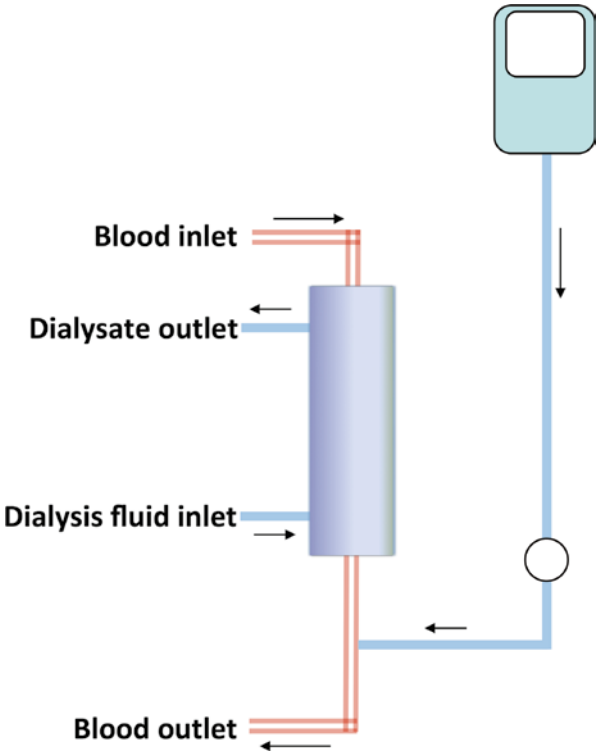


Fig. 2.8 Schematic representation of acetate free biofiltration (AFB)

on the dialysis fluid pathway between the two dialyzers to induce TMP variations and modulate UF in the first dialyzer and backfiltration in the second one [75]. Studies have shown that DHF-HDF with very high Q_B (450–650 ml/min) may provide higher removal of small molecules than standard HD and HF over shorter treatment time [76], and β2-m clearance similar to that in on-line HDF [77, 78]. Increased treatment cost and scarce data about long term effects [76] have limited the diffusion of DHF-HDF, which might provide the benefits of convective therapy to patients in situations where on-line techniques cannot be implemented [78].

Acetate Free Biofiltration (AFB)

This modality was proposed in 1984 as the first HDF technique employing buffer-free dialysis solutions [79, 80]. Correction of acidosis was obtained with infusion in postdilution mode of a solution of sodium bicarbonate supplied in bags at fixed concentration of 120, 145 or 167 mmol/l at a rate of 8–10 l/session (Fig. 2.8). An automatic control system was implemented on dedicated dialysis machines to balance infusion to UF rate. The use of polyacrylonitrile hollow-fiber dialyzers with consistent absorptive power [81] and the absence of acetate resulted in reduced stimulation of inflammatory mediators [82]. Other encouraging traits have been

added over the years, such as the possibility to modulate the concentration of potassium in the dialysate, thus reducing the risk of arrhythmias [83–85], and the possibility to monitor blood volume changes during treatment, thereby reducing intradialytic hypotension episodes and predialysis systolic blood pressure values [86]. Nowadays AFB retains an historical value as one of the first alternative convective therapies but it can hardly be included in modern convective therapies because of the low convective volume it can provide [86], which is comparable to the amount of internal filtration in high-flux HD [30].

Conclusion

On-line post-dilution HDF is at present the most widespread infusion mode in HDF and commonly held as the most efficient in removing middle molecules. The exciting results of this technique in terms of prolonged patient survival may depend on several factors, such as the high biocompatibility of the systems and the dialysate/infusate produced on-line which reduce the chronic inflammatory status of dialysis patients, and the better hemodynamic stability which prevents episodes of severe ischemic cardiac damage. Among those factors, high convective volume and, thus, enhanced middle and small molecular weight solute removal, appears to play an important role and it may only be achieved with the use of high-flux, highly permeable membranes and high blood flow rates. For further reading see Chaps. 16 and 23. Alternative convective and mixed convective-diffusive therapies exploiting the more common mechanisms of solute transport in different ways have been reviewed here. Alternative convective therapies may play a role in enhancing convective removal in definite settings when post dilution HDF fails. Clinical validation with larger numbers and longer follow-up is necessary for an extended application.

Teaching Points II

- Different treatments are described in which convection plays a role:
  - *Internal hemodiafiltration:* solute removal by convection occurring during treatment with high-flux dialyzers, which is compensated by backfiltration of (ultrapure) dialysis fluid.
  - *Hemofiltration*: pure convective solute transport (ultrafiltration) without solute exchange by diffusion in the absence of dialysate flow. The ultrafiltrate is replaced online or offline by sterile substitution fluid
  - *Hemodiafiltration:* solute removal through both convection (hemofiltration) and diffusion (hemodialysis). The ultrafiltrate is replaced online or offline by sterile substitution fluid
- Different modes of hemodiafiltration:
  - *Post-dilution (online) HDF*: Sterile substitution fluid is produced online from the ultrapure dialysate and infused after the filter to replace

the amount of ultrafiltrate, minus weight gain during the interdialytic interval. Most widespread infusion mode in HDF and currently considered as the most efficient modality for removing middle molecules.
- *Pre-dilution (online) HDF*: Sterile substitution fluid is produced on-line and infused before the filter to replace the excess fluid that is extracted from the blood of the patients. Pre-dilution substitution prevents hemoconcentration, but results in the dilution of plasma solute concentrations, thereby reducing the cumulative solute transfer.
- *Mixed HDF:* sterile replacement fluid is simultaneously infused to a variable ratio at the inlet and outlet port of the dialyzer.
- *Mid-dilution HDF*: dedicated hemodiafilters are used, with infusion of sterile substitution fluid through a middle- and a post-dilution infusion port.
- *HDF with endogenous reinfusion*: using a two-chamber filter and a sorbent cartridge, isolated UF takes place through the high-flux membrane of the first chamber. The ultrafiltrate is 'regenerated' while flowing through a sorbent cartridge and infused in the second chamber as endogenous replacement solution. Here, diffusion occurs through a low-flux membrane.
- *Push/pull hemodiafiltration*: alternate fast cycles of UF (pull) and backfiltration (push) of dialysate are performed through a high-flux dialyzer, using a double-cylinder piston pump (push/pull pump) implemented on the effluent dialysate line.
- *Double high-flux hemodiafiltration:* two high-flux dialyzers are placed in series; fluid and solutes are removed in the first dialyzer, while backfiltration of dialysate takes place in the second dialyzer.
- *Acetate Free Biofiltration (AFB):* a mode of offline post-dilution HDF, in which the bicarbonate substitution fluid is supplied in bags.

References

1. Henderson LW, Besarab A, Michaels AS, Bluemle LW. Blood purification by ultrafiltration and fluid replacement (diafiltration). Trans Am Soc Artif Intern Organs. 1967;13:216–26.
2. 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;85:355–71.
3. Henderson LW, Colton CK, Ford CA. Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. J Lab Clin Med. 1975;85:372–91.
4. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schutterle G. Hemodiafiltration: a new alternative to hemofiltration and conventional hemodialysis. Artif Organs. 1978;2:150–3.
5. Quellhorst E. Long-term follow up in chronic hemofiltration. Int J Artif Organs. 1983;6: 115–20.
6. Henderson LW. Biophysics of ultrafiltration and hemofiltration. In: Maher JF, editor. Replacement of renal function by dialysis. Dordrecht: Kluwer; 1989. p. 300–26.
7. Hoenich NA. Membranes and filters for haemodiafiltration. Contrib Nephrol. 2007;158:57–67.
8. Bosch T, Schmidt B, Samtleben W, Gurland HJ. Effect of protein adsorption on diffusive and convective transport through polysulfone membranes. Contrib Nephrol. 1985;46:14–22.

9. Rockel A, Hertel J, Fiegel P, Abdelhamid S, Panitz N, Walb D. Permeability and secondary membrane formation of a high flux polysulfone hemofilter. Kidney Int. 1986;30:429–32.
10. Vilker VL, Colton CK, Smith KA. Concentration polarization in protein ultrafiltration. Am Inst Chem Eng. 1981;27:632–6.
11. Vilker VL, Colton CK, Smith KA, Green DL. The osmotic pressure of concentrated protein and lipoprotein solutions and its significance to ultrafiltration. J Membr Sci. 1984;20:63–77.
12. Lornoy W, Becaus I, Billiouw JM, Sierens L, Van Malderen P. Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. Am J Nephrol. 1998;18:105–8.
13. Floege J, Granolleras C, Deschodt G, et al. High-flux synthetic versus cellulosic membranes for beta 2-microglobulin removal during hemodialysis, hemodiafiltration and hemofiltration. Nephrol Dial Transplant. 1989;4:653–7.
14. Kim ST. Characteristics of protein removal in hemodiafiltration. Contrib Nephrol. 1994;108:23–37.
15. Morti SM, Zydney AL. Protein-membrane interactions during hemodialysis: effects on solute transport. ASAIO J. 1998;44:319–26.
16. Ronco C, Heifetz A, Fox K, et al. Beta 2-microglobulin removal by synthetic dialysis membranes. Mechanisms and kinetics of the molecule. Int J Artif Organs. 1997;20:136–43.
17. David S, Cambi V. Hemofiltration: predilution versus postdilution. Contrib Nephrol. 1992;96:77–85.
18. Michaels AS. Operating parameters and performance criteria for hemodialyzers and other membrane-separation devices. Trans Am Soc Artif Intern Organs. 1966;12:387–92.
19. Wizemann V, Kulz M, Techert F, Nederlof B. Efficacy of haemodiafiltration. Nephrol Dial Transplant. 2001;16 Suppl 4:27–30.
20. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. J Am Soc Nephrol. 2000;11:2344–50.
21. Hauk M, Kuhlmann MK, Riegel W, Kohler H. In vivo effects of dialysate flow rate on Kt/V in maintenance hemodialysis patients. Am J Kidney Dis. 2000;35:105–11.
22. Leypoldt JK, Cheung AK, Agodoa LY, Daugirdas JT, Greene T, Keshaviah PR. Hemodialyzer mass transfer-area coefficients for urea increase at high dialysate flow rates. The Hemodialysis (HEMO) study. Kidney Int. 1997;51:2013–7.
23. Jaffrin MY, Ding LH, Laurent JM. Simultaneous convective and diffusive mass transfers in a hemodialyser. J Biomech Eng. 1990;112:212–9.
24. Bouman CS, van Olden RW, Stoutenbeek CP. Cytokine filtration and adsorption during pre- and postdilution hemofiltration in four different membranes. Blood Purif. 1998;16:261–8.
25. Lonnemann G, Koch KM, Shaldon S, Dinarello CA. Studies on the ability of hemodialysis membranes to induce, bind, and clear human interleukin-1. J Lab Clin Med. 1988;112:76–86.
26. Clark WR, Hamburger RJ, Lysaght MJ. Effect of membrane composition and structure on solute removal and biocompatibility in hemodialysis. Kidney Int. 1999;56:2005–15.
27. Clark WR, Macias WL, Molitoris BA, Wang NH. Membrane adsorption of beta 2-microglobulin: equilibrium and kinetic characterization. Kidney Int. 1994;46:1140–6.
28. Clark WR, Macias WL, Molitoris BA, Wang NH. Plasma protein adsorption to highly permeable hemodialysis membranes. Kidney Int. 1995;48:481–8.
29. Ronco C. Backfiltration in clinical dialysis: nature of the phenomenon, mechanisms and possible solutions. Int J Artif Organs. 1990;13:11–21.
30. Ronco C, Orlandini G, Brendolan A, Lupi A, La GG. Enhancement of convective transport by internal filtration in a modified experimental hemodialyzer: technical note. Kidney Int. 1998;54:979–85.
31. Lucchi L, Fiore GB, Guadagni G, et al. Clinical evaluation of internal hemodiafiltration (iHDF): a diffusive-convective technique performed with internal filtration enhanced high-flux dialyzers. Int J Artif Organs. 2004;27:414–9.
32. Righetti M, Filiberti O, Ranghino A, et al. Internal hemodiafiltration versus low-flux bicarbonate dialysis: results from a long-term prospective study. Int J Artif Organs. 2010;33:796–802.
33. Altieri P, Sorba G, Bolasco P, et al. Predilution haemofiltration – the Second Sardinian Multicentre Study: comparisons between haemofiltration and haemodialysis during identical

Kt/V and session times in a long-term cross-over study. Nephrol Dial Transplant. 2001;16: 1207–13.
34. Altieri P, Sorba GB, Bolasco PG, et al. On-line predilution hemofiltration versus ultrapure high-flux hemodialysis: a multicenter prospective study in 23 patients. Sardinian Collaborative Study Group of On-Line Hemofiltration. Blood Purif. 1997;15:169–81.
35. Fox SD, Henderson LW. Cardiovascular response during hemodialysis and hemofiltration: thermal, membrane, and catecholamine influences. Blood Purif. 1993;11:224–36.
36. Henderson LW. Hemodynamic instability during different forms of dialysis therapy: do we really know why? Blood Purif. 1996;14:395–404.
37. van Kuijk WH, Hillion D, Savoiu C, Leunissen KM. Critical role of the extracorporeal blood temperature in the hemodynamic response during hemofiltration. J Am Soc Nephrol. 1997;8:949–55.
38. De Vries PM, Olthof CG, Solf A, et al. Fluid balance during haemodialysis and haemofiltration: the effect of dialysate sodium and a variable ultrafiltration rate. Nephrol Dial Transplant. 1991;6:257–63.
39. Locatelli F, Altieri P, Andrulli S, et al. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol. 2010;21:1798–807.
40. Pedrini LA, De Cristofaro V, Pagliari B, Sama F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000;58:2155–65.
41. Ahrenholz P, Winkler RE, Ramlow W, Tiess M, Muller W. On-line hemodiafiltration with pre- and postdilution: a comparison of efficacy. Int J Artif Organs. 1997;20:81–90.
42. Cheung AK, Rocco MV, Yan G, et al. Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. J Am Soc Nephrol. 2006;17:546–55.
43. Canaud B, Bragg-Gresham JL, Marshall MR, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int. 2006;69:2087–93.
44. Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
45. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF study. Nephrol Dial Transplant. 2013;28:192–202.
46. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
47. Jenkins RD, Funk JE, Chen B, Golper TA. Operational instability in extracorporeal filtration of blood. Blood Purif. 1992;10:292–308.
48. Pedrini LA, Zerbi S. Mixed-dilution hemodiafiltration. Contrib Nephrol. 2007;158:123–30.
49. Cheung AK, Alford MF, Wilson MM, Leypoldt JK, Henderson LW. Urea movement across erythrocyte membrane during artificial kidney treatment. Kidney Int. 1983;23:866–9.
50. Pedrini LA, De Cristofaro V. On-line mixed hemodiafiltration with a feedback for ultrafiltration control: effect on middle-molecule removal. Kidney Int. 2003;64:1505–13.
51. Pedrini LA, De Cristofaro V, Pagliari B, Filippini M, Ruggiero P. Optimization of convection on hemodiafiltration by transmembrane pressure monitoring and biofeedback. Contrib Nephrol. 2002;137:254–59
52. Pedrini LA, Cozzi G, Faranna P, et al. Transmembrane pressure modulation in high-volume mixed hemodiafiltration to optimize efficiency and minimize protein loss. Kidney Int. 2006;69:573–9.
53. Creput C, Toledano D, Petitclerc T. Ionic dialysance and determination of Kt/V in on-line hemodiafiltration with simultaneouspre- and post-dilution. Int J Artif Organs. 2013;36: 327–34.
54. de Sequera P, Albalate M, Perez-Garcia R, et al. A comparison of the effectiveness of two online haemodiafiltration modalities: mixed versus post-dilution. Nefrologia. 2013;33: 779–87.
55. Potier J, Le RF, Faucon JP, et al. Elevated removal of middle molecules without significant albumin loss with mixed-dilution hemodiafiltration for patients unable to provide sufficient blood flow rates. Blood Purif. 2013;36:78–83.

56. Kuhlmann MK. Phosphate elimination in modalities of hemodialysis and peritoneal dialysis. Blood Purif. 2010;29:137–44.
57. Krieter DH, Falkenhain S, Chalabi L, Collins G, Lemke HD, Canaud B. Clinical cross-over comparison of mid-dilution hemodiafiltration using a novel dialyzer concept and post-dilution hemodiafiltration. Kidney Int. 2005;67:349–56.
58. Feliciani A, Riva MA, Zerbi S, et al. New strategies in haemodiafiltration (HDF): prospective comparative analysis between on-line mixed HDF and mid-dilution HDF. Nephrol Dial Transplant. 2007;22:1672–9.
59. Santoro A, Ferramosca E, Mancini E, et al. Reverse mid-dilution: new way to remove small and middle molecules as well as phosphate with high intrafilter convective clearance. Nephrol Dial Transplant. 2007;22:2000–5.
60. Pedrini LA, Feliciani A, Zerbi S, Cozzi G, Ruggiero P. Optimization of mid-dilution haemodiafiltration: technique and performance. Nephrol Dial Transplant. 2009;24:2816–24.
61. Eloot S, Dhondt A, Van LM, Waterloos MA, Vanholder R. Removal of water-soluble and protein-bound solutes with reversed mid-dilution versus post-dilution haemodiafiltration. Nephrol Dial Transplant. 2012;27:3278–83.
62. de Francisco AL, Botella J, Escallada R, et al. Haemodiafiltration with sorbent-regenerated ultrafiltrate as replacement fluid: a multicenter study. Nephrol Dial Transplant. 1997;12: 528–34.
63. de Francisco AL, Pinera C, Heras M, et al. Hemodiafiltration with on-line endogenous reinfusion. Blood Purif. 2000;18:231–6.
64. Ghezzi PM, Botella J, Sartoris AM, Gervasio R, Diez C. Use of the ultrafiltrate obtained in two-chamber (PFD) hemodiafiltration as replacement fluid. Experimental ex vivo and in vitro study. Int J Artif Organs. 1991;14:327–34.
65. Ghezzi PM, Gervasio R, Tessore V, Sartoris AM, Botella J. Hemodiafiltration without replacement fluid. An experimental study. ASAIO J. 1992;38:61–5.
66. Sanz-Moreno C, Botella J. Hemodiafiltration in two chambers without replacement fluid: a clinical study. Artif Organs. 1995;19:407–10.
67. Wratten ML, Ghezzi PM. Hemodiafiltration with endogenous reinfusion. Contrib Nephrol. 2007;158:94–102.
68. Calo LA, Naso A, Carraro G, et al. Effect of haemodiafiltration with online regeneration of ultrafiltrate on oxidative stress in dialysis patients. Nephrol Dial Transplant. 2007;22:1413–9.
69. Borrelli S, Minutolo R, De NL, et al. Intradialytic changes of plasma amino acid levels: effect of hemodiafiltration with endogenous reinfusion versus acetate-free biofiltration. Blood Purif. 2010;30:166–71.
70. Maeda K, Shinzato T. Push/pull hemodiafiltration: technical aspects and clinical effectiveness. Nephron. 1995;71:1–9.
71. Miwa M, Shinzato T. Push/pull hemodiafiltration: technical aspects and clinical effectiveness. Artif Organs. 1999;23:1123–6.
72. Shinzato T, Miwa M, Kobayakawa H, et al. Effectiveness of new push/pull hemodiafiltration for arthralgia in long-term hemodialysis patients. Contrib Nephrol. 1995;112:111–8.
73. Shinzato T, Maeda K. Push/pull hemodiafiltration. Contrib Nephrol. 2007;158:169–76.
74. von Albertini B, Miller JH, Gardner PW, Shinaberger JH. Performance characteristics of high flux haemodiafiltration. Proc Eur Dial Transplant Assoc Eur Ren Assoc. 1985;21:447–53.
75. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58:809–17.
76. Bosch JP, Lew SQ, Barlee V, Mishkin GJ, von Albertini B. Clinical use of high-efficiency hemodialysis treatments: long-term assessment. Hemodial Int. 2006;10:73–81.
77. Susantitaphong P, Tiranathanagul K, Katavetin P, et al. Efficacy of convective-controlled double high-flux hemodiafiltration versus on-line hemodiafiltration: 1-year prospective study. Blood Purif. 2010;29:35–43.
78. Tiranathanagul K, Yossundharakul C, Techawathanawanna N, et al. Comparison of middle-molecule clearance between convective control double high-flux hemodiafiltration and on-line hemodiafiltration. Int J Artif Organs. 2007;30:1090–7.

79. Santoro A, Ferrari G, Spongano M, Badiali F, Zucchelli P. Acetate-free biofiltration: a viable alternative to bicarbonate dialysis. Artif Organs. 1989;13:476–9.
80. Zucchelli P, Santoro A, Raggiotto G, Degli EE, Sturani A, Capecchi V. Biofiltration in uremia: preliminary observations. Blood Purif. 1984;2:187–95.
81. Galli G, Panzetta G. Acetate free biofiltration (AFB): from theory to clinical results. Clin Nephrol. 1998;50:28–37.
82. Amore A, Cirina P, Mitola S, et al. Acetate intolerance is mediated by enhanced synthesis of nitric oxide by endothelial cells. J Am Soc Nephrol. 1997;8:1431–6.
83. Munoz RI, Montenegro J, Salcedo A, et al. Effect of acetate-free biofiltration with a potassium-profiled dialysate on the control of cardiac arrhythmias in patients at risk: a pilot study. Hemodial Int. 2008;12:108–13.
84. Santoro A, Mancini E, Fontanazzi F, Paolini F. Potassium profiling in acetate-free biofiltration. Contrib Nephrol. 2002;137:260–67
85. Severi S, Vecchietti S, Cavalcanti S, Mancini E, Santoro A. Electrocardiographic changes during hemodiafiltration with different potassium removal rates. Blood Purif. 2003;21:381–8.
86. Tessitore N, Santoro A, Panzetta GO, et al. Acetate-free biofiltration reduces intradialytic hypotension: a European multicenter randomized controlled trial. Blood Purif. 2012;34: 354–63.

Chapter 3
Water Treatment and Safety Requirements

Richard A. Ward and James E. Tattersall

Abstract On-line haemodiafiltration differs from other forms of haemodialysis in that up to 20 L/h of dialysis fluid can be infused directly into the bloodstream during each treatment. That infused fluid must be free of chemical contaminants, sterile and pyrogen-free. Compliance with that requirement cannot be demonstrated by testing at the time of infusion. Instead, the infused fluid must be prepared using equipment that has been validated to produce sterile and pyrogen-free fluid when operated in accordance with the machine manufacturer's instructions. It is the responsibility of the user of the machine to ensure those instructions are followed, including providing the dialysis machine with water and concentrates that meet the specifications set forth by the machine manufacturer. Properly designed systems for water treatment and distribution and concentrate preparation are central to achieving that goal. In addition, those systems must be subject to rigorous quality control that includes maintenance practices designed to prevent contamination of the dialysis and infusion fluids, coupled to monitoring that verifies the adequacy of the system design and maintenance program.

Keywords Dialysis fluid quality • Infusion fluid quality • Water treatment • Microbiological contaminants • Endotoxin • Equipment maintenance

Introduction

Like other forms of haemodialysis, HDF exposes patients to 30–60 l of dialysis fluid for each hour of treatment. Patients may be harmed by any contaminants in that dialysis fluid since water-soluble contaminants can diffuse across the dialyser

R.A. Ward, PhD
Kidney Disease Program, University of Louisville, Louisville, USA

J.E. Tattersall, MB BS, MD (✉)
Department of Renal Medicine, Leeds Teaching Hospitals, Leeds, West Yorkshire LS9 7TF, UK
e-mail: jamestattersall@nhs.net

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_3

membrane from the dialysis fluid to the blood as easily as uraemic toxins diffuse from the blood to the dialysis fluid. In this respect, the risk is the same for low-flux dialysis, high-flux dialysis and HDF and the concentration of any potentially toxic solute in the dialysis fluid must be reduced to safe levels regardless of the therapy.

Unlike other forms of haemodialysis, in on-line HDF, up to 20 L/h of dialysis fluid can be infused directly into the blood, bypassing the dialyser membrane. This fluid for infusion is required to be sterile and pyrogen-free. Since that requirement necessitates levels of microbiological contaminants far below detection limits, dialysis machines for HDF incorporate a process validated to produce sterile, pyrogen-free infusion fluid from standard dialysis fluid [1].

This chapter reviews the contaminants commonly encountered in preparing fluids for HDF, the hazards associated with those contaminants, and the steps that can be taken to ensure that they do not exceed safe levels in the dialysis and infusion fluids.

Contaminants Encountered in the Preparation of Fluids for HDF

Low-Molecular Weight Contaminants

A number of low-molecular-weight substances commonly found in drinking water supplies are toxic to haemodialysis patients. These substances, some of which are added to the drinking water supply for public health reasons, have been long known to cause a variety of toxicities, including anaemia (chloramine, aluminium), arrhythmias (fluoride), bone disease (aluminium), and a fatal encephalopathy (aluminium) [2]. The maximum allowable concentrations for these low-molecular-weight contaminants in water used to prepare dialysis fluid, and in the final dialysis fluid, are approximately tenfold lower than allowed in drinking water [3, 4]. This is because of the large volumes of fluid involved, the non-selective nature of toxin transfer across the dialyser membrane, and the lack of any excretory kidney function to eliminate any toxins that do enter the bloodstream (Table 3.1).

Microbial Contaminants

Microbial contaminants of water used for dialysis include viable microorganisms (e.g. bacteria, viruses, fungi, algae, prions) and organic fragments released by those microorganisms during their lifecycle and death. Viable microorganisms may be capable of causing infection, while microbial products can cause an inflammatory response in the patient. Safe limits have been set for the level of microbiological contaminants in dialysis fluid [5] (Table 3.2).

Table 3.1 Comparison of standards for drinking water and dialysis water

Contaminant	WHO recommendations for drinking water (mg/L) [3]	ISO 11663:2014 standards dialysis water (mg/L) [4]
Aluminium	0.1	0.01
Arsenic	0.01	0.005
Barium	0.7	0.1
Cadmium	0.003	0.001
Calcium	200	2.0
Total chlorine	5	0.1
Chromium	0.05	0.014
Copper	2	0.1
Fluoride	1.5	0.2
Lead	0.01	0.005
Magnesium	50	4.0
Mercury	0.006	0.0002
Nitrate (N)	50	2.0
Potassium	–	8.0
Selenium	0.04	0.09
Silver[a]	0.05	0.005
Sodium[a]	200	70.0
Sulphate	–	100.0
Zinc	5	0.1

[a]Canadian standard (WHO determined evidence inadequate to set safe limit)

Table 3.2 Maximum allowable levels of microbiological contaminants in dialysis fluids

	Endotoxin EU/mL	Bacteria CFU/mL
Standard dialysis fluid	<0.5	<100
Ultrapure dialysis fluid	<0.03	<0.1
Sterile, pyrogen-free infusion fluid[a]	<0.03	<0.000001

Based on data from Ref. [5]

[a]Must be ensured by proper operation of a validated system, verified by the manufacturer

Viable bacteria are monitored by culturing fluid samples in a low-nutrient medium in the dark, at room temperature, for several days. Viable bacterial contamination is quantified by counting the colonies growing on the medium and reporting as colony-forming units per ml (CFU/mL).

The microbial fragments contaminating dialysis water vary widely in size and composition. The components likely to cause inflammation are those which are small enough to pass through the dialyser membrane into the bloodstream, yet large enough to provoke an inflammatory response. Endotoxin, a lipopolysaccharide originating from the bacterial cell wall, is a representative inflammatory microbial contaminant. Since endotoxin molecules vary in size, endotoxin contamination is typically measured as its inflammatory potential in Endotoxin Units/mL (EU/mL) using the *Limulus amebocyte* lysate (LAL) assay. LAL assay kits,

capable of detecting as little as 0.001 EU/mL are commercially available. Short fragments of bacterial DNA are another potential contaminant originating from bacterial colonization of the treated water distribution system. These fragments have been shown to induce inflammation. Compared to endotoxin, they are smaller molecules and can more easily pass through a dialyser or filter membrane. There is currently no test that can be used to routinely monitor these DNA levels [6].

In conventional haemodialysis, the dialysis fluid is separated from the blood by the dialyser membrane. Because microbial contaminants are typically large solutes which diffuse slowly, they do not pass through low-flux dialyser membranes to a significant extent. For that reason, it is considered acceptable for the dialysis fluid to contain up to 100 viable bacteria/mL and up to 0.25 EU/mL of endotoxin. In high-flux dialysis, the membrane is typically about 50 μm thick and is highly porous. Viable bacteria are still too large to pass through those membranes. However, naturally occurring endotoxins are of variable size and some are small enough to potentially pass through the pores. Nevertheless, a high flux dialyser is an effective barrier to endotoxin because endotoxin is absorbed onto the membrane surfaces before it can reach the blood [7].

In high-flux dialysers, there is inevitably reverse ultrafiltration at the downstream end of the blood compartment, so-called 'backfiltration'. This is because flow in the blood compartment is driven by higher pressure at the upstream end, compared to pressure downstream. This pressure difference also causes ultrafiltration of fluid from blood into the dialysis fluid compartment at the upstream end, balanced by reverse filtration in the opposite direction at the downstream end. Reverse ultrafiltration can enhance transfer of higher molecular weight toxins from dialysis fluid to blood across the membrane (Fig. 3.1). Standard dialysis fluid may contain up to 0.25 EU/mL and up to 2 L of dialysis fluid may enter the blood per hour due to backfiltration in high-flux dialysis. Assuming a 100-fold reduction of endotoxin concentration in the reverse filtrate due to absorption to the membrane, the dose of endotoxin to the patient would be 5 EU/h. That dose is a dose approximately 100 times lower than that thought to induce acute adverse effects (400 EU/h). Nevertheless, it is now recommended to use ultrapure dialysis fluid, which contains <100 CFU/L of bacteria and <0.03 EU/mL of endotoxin [5], for all modes of haemodialysis [8].

Adverse Effects of Microbial Contaminants

Acute Effects of Endotoxin

Drinking water supplies are treated to render all microorganisms non-viable (for example, by killing them with chlorine) so that they are not capable of causing infection. However, fragments of the killed bacteria remain in the water and drinking water can contain as much as 30 EU/mL of endotoxin. The gastrointestinal system will inactivate orally ingested endotoxins so that they do not cause inflammation. However, even small amounts of endotoxin will induce an inflammatory response if they enter the body by another route, such as injection. Studies with human volunteers have

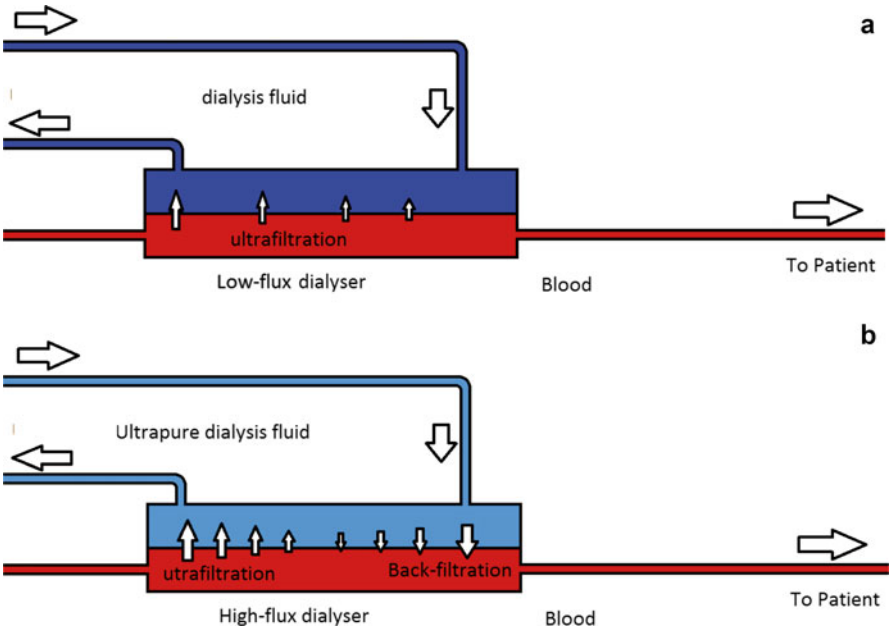


Fig. 3.1 The upper panel shows the difference in ultrafiltration between low-flux (**a**) and high-flux dialyser (**b**). With high-flux, there is back filtration from dialysis fluid to blood at the blood outlet end

shown that acute injection of endotoxin causes fever, hypotension and increases in leukocyte numbers and IL-6 concentrations. The minimum dose required to produce observable effects in 50 % of subjects was 4 EU/kg body weight. Informed by these studies, the FDA has set the maximum permissible mass of endotoxin which can be injected into the blood at 5 EU/kg. This is the amount of endotoxin present in approximately 0.2 mL of tap water. Because there are mechanisms to clear pyrogens from the blood, the time over which endotoxin is delivered is also important. Acute toxic effects of endotoxin (fever, hypotension) occur when endotoxin is delivered at a rate greater than 5 EU/kg/h [9]. For a patient weighing 80 kg, this would be 400 EU/h.

The hypotension caused by endotoxin injection is partly caused by vasodilatation and partly by transfer of fluid out of the vascular compartment due to altered capillary permeability and pressure. These changes are likely to be more serious during dialysis as they would oppose the vasoconstriction and vascular re-filling required to maintain blood pressure as fluid is removed by ultrafiltration.

Chronic Effects of Inflammation

Cardiovascular disease is now commonly thought to be caused or exacerbated by inflammation. The inflammation associated with cardiovascular disease is at a much lower level than would cause acute symptoms. Inflammatory markers have been associated with cardiovascular mortality in the general population and in dialysis patients.

Endothelial dysfunction induced by inflammation, macrophage migration into the arterial walls, and macrophage apoptosis are now seen as the key steps in the development of atherosclerotic plaques. Cardiovascular calcification is particularly common in dialysis patients and is shown to be associated with increased mortality. Cardiovascular calcification is now considered to be part of the inflammatory response [10].

Repeated hypotension during dialysis is very common. The hypotension induces cerebral and myocardial ischaemia. This contributes to organ dysfunction, including myocardial stunning which contributes to cardiac mortality. Inflammation is one of the causes of the hypotension [11].

Dialysis patients commonly exhibit a syndrome of malnutrition, inflammation and atherosclerosis (the MIA syndrome). Inflammatory cytokines cause both atherosclerosis and malnutrition which, in turn, cause further inflammation creating a self-perpetuating cycle associated with poor outcome [12].

In an observational study, patients dialysing in facilities with higher endotoxin levels had significantly increased mortality [13, 14]. Improvement in the microbiological quality of dialysis water has been shown to be associated with a reduction in inflammatory markers [15, 16] and an improvement in response to erythropoietin [17].

Achieving Fluid Quality for HDF

Taken together, the observations presented in the previous section highlight the importance of maintaining a high level of purity in the fluids used for HDF. That goal pursued at every stage of fluid preparation, from treatment of the incoming drinking water to generation of replacement fluid.

Water Treatment

Water treatment systems designed to produce water of the quality required for dialysis, including HDF, are generally obtained from specialized vendors, typically use a combination of relatively non-specific purification steps to reduce the level of all potential contaminants by a factor of about 100, and are almost always centred on reverse osmosis as the primary purification process. Optimum performance of the reverse osmosis unit is ensured by pre-treating the feed water to the unit. The types of pre-treatment will depend on the quality of the water entering the dialysis facility. For example, where the supply water is hard, the water treatment system should incorporate a softener to remove calcium and magnesium that would otherwise foul the reverse osmosis membranes and, where the water supply is disinfected with chlorine or chloramine, the water treatment system should include a means of removing those contaminants, such as carbon filtration.

The efficacy of each stage of the process is monitored by measuring the concentration of a single representative contaminant downstream of each stage: softener

function is tested by a hardness test or calcium ion-specific electrode; the efficacy of carbon filtration is tested by measuring the total chlorine concentration in the water exiting the carbon bed; and, the efficacy of reverse osmosis is tested by measuring the conductivity of the treated water. The water treatment system and its operation should incorporate sufficient redundancy and monitoring so that failure at a single point is detected and corrected while maintaining adequate water quality.

Maintaining the chemical purity of the water between the end of the water treatment system and the point at which it enters the HDF machine is ensured by constructing the water distribution system from inert materials, such as cross-linked polyethylene, Teflon, or stainless steel.

The maximum allowable levels of microbiological contaminants in water used to prepare replacement fluid for HDF are set by the manufacturer of the HDF equipment [18, 19] and are generally the same as those recommended for standard hemodialysis [4]. A well-functioning water treatment system for dialysis should produce water free of any microbial contaminants as it emerges from the reverse osmosis unit and enters the treated water distribution system. Some authorities recommend the use of two-stage reverse osmosis to prevent microbial contaminants from entering the treated water distribution system; however, available evidence suggests it could be unnecessary to do so [20].

Since the water treatment system produces water that is also free of chlorine or chloramine, any bacteria that do gain entry to the treated water distribution system can colonize the distribution system and contaminate the water entering the dialysis machine. Thus, to achieve high-quality dialysis fluid it is important to focus on preventing bacterial entry and controlling bacterial growth within the system. Bacteria can gain entry to the system via contaminated ports or connectors. Bacteria can also proliferate in the complex fluid pathway of the dialysis machine. In particular, *Pseudomonas* species of bacteria thrive in the low-nutrient, low light, room-temperature aqueous environment of the dialysis water system. *Pseudomonas sp.* can secrete a protein- and polysaccharide-containing slime which facilitates adherence of colonies to the internal surfaces of the piping. That biofilm will shed microbial fragments and occasional viable organisms into the dialysis water, especially after disinfection.

Minimizing the development of biofilm and routinely achieving low levels of microbial contaminants in the water entering the HDF machine depends on both the design and maintenance of the water distribution system. Some key design features related to minimizing biofilm growth are summarized in Table 3.3. For biofilm control, the water distribution system is best configured as direct feed, where the water leaving the reverse osmosis unit flows directly to the HDF machines with any surplus being returned to the inlet of the reverse osmosis unit. Direct feed systems are often impractical, however, and in many situations an indirect feed system incorporating a storage tank will be necessary, either to deal with fluctuating demands for water or to enable the pressure in the distribution system to be boosted. No matter which configuration is used, the water distribution system should be fabricated from a material that allows disinfection with hot water or water containing ozone.

Table 3.3 Design strategies for minimizing microbiological contamination in the preparation of dialysis fluid

Design feature	Benefit
The final stage in the water treatment system should provide a barrier against microbiological contaminants; for example, reverse osmosis or an endotoxin-retentive filter	Prevents entry of bacteria which proliferate in the water treatment system following removal of disinfectants from the potable water supply
Reverse osmosis membranes should be of the hygienic or "full-fit" type	Bacteria can bypass the brine seals used in older types of membrane module
The water distribution system should be configured as the shortest possible loop without branches or dead-ends	Avoids stagnant areas that disinfectants have difficulty reaching
A direct feed water distribution system should be used where practical	Avoids the use of a storage tank where water can be semi-stagnant around the periphery and which can be difficult to disinfect
For direct feed systems, a means of preventing retrograde flow from the inlet line to the reverse osmosis system to the returning treated water distribution loop	Prevents untreated water from entering the treated water distribution system if there is a transient fluctuation in pressure
If a water storage tank is used (indirect feed system), it should have the smallest practical volume and have an easily implemented means of disinfection	Maximizes fluid turn-over in the tank and minimizes stagnation
The water distribution system should be constructed of materials compatible with disinfection by hot water or water containing ozone	Disinfection with hot water or water containing ozone allows daily disinfection, which is impractical with chemical disinfectants
There should be an easily implemented method of disinfecting the inlet water line to the HDF machine	This line is not disinfected when the HDF machine is disinfected and is a common site of biofilm formation
Dry powder cartridges should be used for the preparation of bicarbonate concentrate	Avoids the need to store batches of bicarbonate concentrate which are susceptible to proliferation of haloduric organisms
Connectors should be designed to resist contamination and disinfected regularly	Avoids contamination of the dialysis fluid as it enters the dialyser

Concentrates

While preparation of water meeting the specifications of the manufacturer of the HDF machine is a necessary requirement for HDF, it is not sufficient to ensure trouble-free treatments. The concentrates used to prepare the dialysis fluid from which the replacement fluid is generated must also be of high microbiological quality. Here, the concern is with the bicarbonate-containing concentrate since the pH of the acid concentrate is sufficiently low to prevent microbial growth. Bicarbonate-containing concentrates provide a good growth medium for haloduric organisms [21] and preparation of batches of bicarbonate-containing concentrate from water

and powder at the dialysis facility, and distribution of that concentrate to individual HDF machines, can be an important source of contamination. The most effective means of overcoming that risk is to use powder cartridges designed for use with a particular HDF machine to prepare bicarbonate-containing concentrate on-line at the point of use [22]. Systems that prepare bicarbonate-containing concentrate online for multiple HDF machines have been developed, but to date their use appears to be restricted to Japan [23].

Dialysis Fluid

A properly designed and managed dialysis system will produce dialysis fluid which meets the ISO standards shown in Tables 3.1 and 3.2. That fluid will contain less than 0.25 EU/mL of endotoxin. A patient can be exposed to up 50 L/h of the fluid, which could contain 12,500 EU endotoxin. Fortunately the dialysis membrane is a barrier to the endotoxin, preventing most of it from entering the blood. Nonetheless, many believe standard dialysis fluid should be subjected to filtration though an ultrafilter, usually fitted as part of the dialysis machine, to render the dialysis fluid ultrapure; that is, with a maximum endotoxin concentration of less than 0.03 EU/mL and a total exposure of less than 1,500 EU. While ultrafilters effectively reduce endotoxin concentrations by a factor of at least 100, they may not efficiently remove smaller microbiological contaminants such as DNA fragments [24, 25]. Therefore, a system should not rely on ultrafilters, alone, to maintain fluid quality. It is still necessary to keep bacterial growth within the system to a minimum so that the fluid upstream of the filter conforms to standard quality.

The last point at which the dialysis fluid can be contaminated is where it enters the dialyser. Standard Hansen connectors can be difficult to clean and disinfect and the use of connectors purposefully designed to minimize contamination [19, 26] is preferred.

In post-dilution HDF, approximately 5 L of dialysis fluid is ultrafiltered from the blood each hour. This could be increased up to 20 L/h in pre-dilution HDF. This 5–20 L/h of ultrafiltrate is balanced by infusing a similar volume of fluid directly into the blood.

The pressure difference across the dialyser membrane required to drive that ultrafiltration, effectively prevents the back-filtration which would occur in high-flux dialysis.

However, to avoid infusing more than 400 EU/h of endotoxin, the infused fluid needs to contain less than 0.02 EU/mL of endotoxin. This is below the limit of detection for many endotoxin assays. Thus, current on-line HDF machines use a validated process based on two stages of filtration. The first stage generates ultrapure dialysis fluid, with endotoxin <0.03 EU/mL. The second stage subjects the ultrapure fluid to further ultrafiltration by a device which has been shown to reduce endotoxin levels by a factor of at least 100. It is not possible to verify that the infusion fluid produced by this two-step process is of the required purity. Instead, the process must have been

validated to show that an adequate quality of the infusion fluid is produced every time the machine is used. The validated process is, in part, controlled and monitored automatically by the dialysis machine. However, the process also requires actions by the machine operator and it is imperative that these actions are preformed strictly in accordance with the manufacturer's instructions for use of the machine.

In post-dilution HDF, the infusate is pumped into the venous bubble trap which is under high pressure. In case of leaks or failure of the infusate pump, there is a risk of blood entering the infusate line, potentially contaminating the upstream fluid pathway which is shared between patients. This could allow transfer of blood-borne viruses between patients if there was a simultaneous failure of the disinfection process. To reduce this risk, there is a non-return valve in the infusate line. In HDF, the uncontrolled, unmonitored back-filtration of high-flux dialysis is replaced by controlled and monitored infusion through the infusate filter. The infusion rate is driven by the infusate pump (Fig. 3.2). The safety of HDF depends on the integrity and sterility of the filter, non-return valves and infusate fluid pathway.

One approach to ensuring this is to replace the valve, infusate filter and the entire fluid pathway downstream of the filter with new, sterile packaged components each treatment (Fig. 3.2, top). In this case, the burden of quality control is shifted partly from user to the manufacturer of the packaged components. The infusate line, valve and filter can be integrated into the blood line so there are no connectors in the sterile fluid pathway.

In an alternative approach (Fig. 3.2, bottom), the infusate filter and part of the sterile fluid pathway is disinfected and tested before each treatment. The disinfection process uses measurable physical conditions (e.g. low pH, high temperature). The dialysis machine software monitors the fluid flow and conditions during the disinfection process. The integrity of the fluid pathway, including valve and filter, is tested automatically by the system by monitoring pressure under defined flow conditions. The filter membrane integrity can be tested by allowing air to enter the filter on one side of the membrane (pressure holding test). An intact wet filter membrane is impervious to air. The machine control software will not allow treatment unless the tests have been passed and the system has been adequately disinfected. The disinfection and testing process can be combined with the testing and disinfection of ultrapure dialysis fluid pathway. In this approach, there is a connector in the sterile part of the infusate line, downstream of the filter. The connector design and operation must minimize the chance of introducing contaminants at this point. This approach has the advantage of reduced cost, as the infusate filter is used multiple times. Disadvantages of this approach include increased complexity of equipment and operation.

System Maintenance

Since the potential sources of contamination of dialysis fluids are so diverse and depend on multiple procedures and equipment, each fluid preparation system faces its own unique challenges. No matter how well the water treatment and

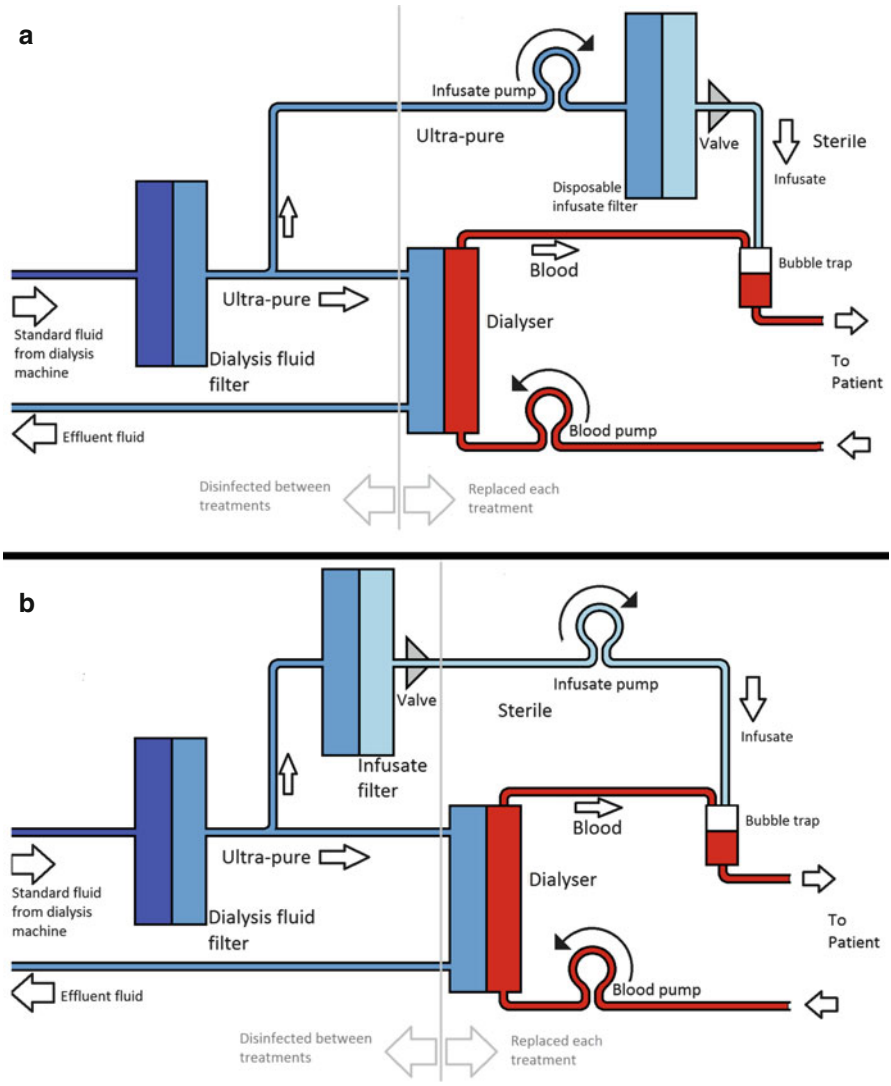


Fig. 3.2 (**a**, **b**) Two designs for HDF

distribution systems are designed, their performance, particularly with regard to microbiological purity, will deteriorate over time unless they are well maintained. The medical director of the dialysis unit is ultimately responsible for the quality of the fluids to which the patients are exposed and it is her or his responsibility to ensure that a maintenance program capable of maintaining the desired quality of the fluids delivered to the patient is established and executed. Guidance on how to achieve this goal has been published as an adjunct to the fluid quality standards [8].

To be successful, a maintenance program must be forward-looking and instituted from first use of the fluid handling systems. The primary goal of the maintenance program is to maintain the systems in such a way that fluid quality is sustained as a routine; it should not be thought of as a means of responding to unacceptable monitoring results. Development of an environment that routinely delivers fluids of the desired quality proceeds through a number of steps [27] (Table 3.4).

The first step should be an initial qualification of the entire fluid handling system. While the initial qualification is best done immediately following installation of a system, it can also be done on an existing system at the time the decision is made to implement an HDF program. The purpose of the initial qualification is to document the system in written form, confirm that there is a written maintenance program for the system, and verify that the staff has received appropriate training on the operation and maintenance of the system. In the case of new systems, it is the time to verify that the system has been installed in accordance with its specifications. Responsibility for the various facets of the operation of the system should be clearly defined at this stage and the qualification should be approved by the person at the dialysis facility with overall responsibility for fluid production. For new systems, that approval often establishes the point at which responsibility for the fluid production systems passes from the vendors who provide and install those systems to the persons with day-to-day responsibility for operation of the dialysis facility. It is important that the disinfection program be initiated as soon as the integrity of the system has been established by pressure testing using filtered air, not fluids which may contaminate the system's internal surfaces.

Table 3.4 Steps in establishing stable fluid production systems

Step	Purpose	Includes
Initial qualification	Define the fluid handling systems and its management	System documentation (Flow diagrams, operating and maintenance manuals)
		Determination of proper installation
		Evidence of proper training
Operational qualification	Demonstration that systems operate as specified	Demonstration that systems operate over intended range of operation
		Demonstration that safety systems operate as intended
		Demonstration that fluid quality specifications are met
Performance qualification	Demonstration that performance is stable over time under routine operating conditions	Intensive monitoring of fluid quality
Routine monitoring	Demonstrate ongoing compliance with fluid quality specifications	Regular monitoring of system components and fluid quality
		Trend analysis of performance data

The initial qualification should be followed by an operational qualification to verify that the system operates as specified, including fluid quality, safety systems and maintenance procedures.

Once the fluid systems have been demonstrated to perform as specified, a period of intensive monitoring should follow to demonstrate that fluid quality is routinely maintained under normal operating conditions. In assessing microbiological quality, it is important to remember that initial negative cultures can be misleading since it can take several weeks before biofilm in the dialysis water distribution system matures to the point that it sheds bacteria into the water.

Once it is clear from the initial qualification phases that the systems are stable and can produce fluid meeting the requirements of the HDF machine manufacturers under normal operating conditions and with the specified maintenance program, ongoing routine monitoring should be performed to ensure continued compliance with the fluid quality requirements. Monitoring data should be subjected to trend analysis to provide advanced information on any changes in system performance so that changes to correct problems can be made prospectively rather than in a reactive manner. This approach is particularly important for the microbiological quality of the fluid since it can be difficult to remove biofilm once it matures.

While the tendency for biofilm formation can be lessened by attention to the design of the distribution system, consistently achieving low levels of microbial contaminants in the water delivered to the HDF machine requires frequent disinfection of all the fluid pathways to minimize biofilm formation. Because biofilm is extremely difficult to eradicate once it has become established, it is key that the disinfection program be designed to prevent biofilm formation rather than eliminate biofilm once it has formed. The preferred means of disinfection is by hot water or water containing ozone. These methods are preferred because, in the case of hot water, there are no residuals or, in the case of ozone, residuals with a very short lifespan. That lack of residuals allows disinfection to be carried out on a daily basis if needed. In contrast, disinfection with chemicals, such as sodium hypochlorite, leaves residuals that require extensive rinsing to remove, thereby limiting disinfection generally to no more than once per week.

An effective ultrafilter will reduce the endotoxin concentration by a factor of at least 100. To remain effective, the system must be properly maintained and operated, since there is the potential for contamination to enter the fluid through the solute additions, connectors, filter membrane defects or bacterial growth downstream of the filter. The filter must be disinfected by a compatible disinfectant and changed at regular intervals as specified by the manufacturer. To reduce the risk of contaminants passing through the filter membrane defects, redundant filters in series may be employed. In an alternative approach, the filter integrity is tested automatically before each use by the system. A typical membrane integrity test would require the filter to hold a pressure difference across the membrane when air has been allowed to enter on one side. An intact membrane should be impervious to air when wet.

Teaching Points

- During online hemodiafiltration, up to 20 L/h of dialysis fluid can be infused directly into the bloodstream.
- This infusion fluid must be free of chemical contaminants, sterile and pyrogen-free.
- This infusion fluid must be prepared with a dialysis machine that has been validated to produce sterile and pyrogen-free fluid.
- The user of the machine is responsible to ensure the machine manufacturer's instructions are followed, including providing the dialysis machine with water and concentrates that meet the specifications as set by the machine manufacturer.
- Properly designed systems for water treatment and distribution, and concentrate preparation are central to produce sterile and pyrogen-free infusion fluid, free of contaminants.
- Water treatment and distribution systems must be subject to rigourous quality control including maintenance practices designed to prevent contamination of the dialysis and infusion fluids.

References

1. Ledebo I. On-line preparation of solutions for dialysis: practical aspects versus safety and regulations. J Am Soc Nephrol. 2002;13:S78–83.
2. Ward RA. Water processing for hemodialysis. A historical perspective. Semin Dial. 1997;10:26–31.
3. World Health Organization. Guidelines for drinking water quality. 4th ed. WHO press, Geneva, Switzerland. 2011.
4. International Organization for Standardization. Water for haemodialysis and related therapies (ISO 13959:2014). Geneva: International Organization for Standardization; 2014.
5. International Organization for Standardization. Quality of dialysis fluid for haemodialysis and related therapies (ISO 11663:2014). Geneva: International Organization for Standardization; 2014.
6. Handelman GJ, Megdal PA, Handelman SK. Bacterial DNA in water and dialysate: detection and significance for patient outcomes. Blood Purif. 2009;27:81–5.
7. Henrie M, Ford C, Andersen M, et al. In vitro assessment of dialysis membrane as an endotoxin transfer barrier: geometry, morphology, and permeability. Artif Organs. 2008;32:701–10.
8. International Organization for Standardization. Guidance for the preparation and quality management of fluids for haemodialysis and related therapies (ISO 23500:2014). Geneva: International Organization for Standardization; 2014.
9. Williams KL. Endotoxins: pyrogens, LAL testing and depyrogenation. 2nd ed. New York: Marcel Dekker Inc; 2001.
10. New SE, Aikawa E. Cardiovascular calcification: an inflammatory disease. Circ J. 2011;75:1305–13.
11. McIntyre CW, Harrison LE, Eldehni MT, et al. Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:133–41.
12. Yao Q, Axelsson J, Heimburger O, et al. Systemic inflammation in dialysis patients with end-stage renal disease: causes and consequences. Minerva Urol Nefrol. 2004;56:237–48.

13. Hasegawa T, Nakai S, Masakane I, et al. Dialysis fluid endotoxin level and mortality in maintenance hemodialysis: a nationwide cohort study. Am J Kidney Dis. 2015. doi:10.1053/j.ajkd.2014.12.009.
14. Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. Nephrol Dial Transplant. 2013;28:438–46.
15. Kwan BC, Chow KM, Ma TK, et al. Effect of using ultrapure dialysate for hemodialysis on the level of circulating bacterial fragment in renal failure patients. Nephron Clin Pract. 2013;123:246–53.
16. Arizono K, Nomura K, Motoyama T, et al. Use of ultrapure dialysate in reduction of chronic inflammation during hemodialysis. Blood Purif. 2004;22:26–9.
17. Sitter T, Bergner A, Schiffl H. Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. Nephrol Dial Transplant. 2000;15:1207–11.
18. Ledebo I. On-line haemodiafiltration: technique and therapy. Adv Ren Replace Ther. 1999;6:195–208.
19. Polaschegg H-D, Roy T. Technical aspects of online hemodiafiltration. In: Ronco C, Canaud B, Aljama P, editors. Hemodiafiltration, Contrib Nephrol, vol. 158. Basel: Karger; 2007. p. 68–79.
20. Penne EL, Visser L, van den Dorpel MA. Microbiological quality and quality control of purified water and ultrapure dialysis fluids for online hemodiafiltration in routine clinical practice. Kidney Int. 2009;76:665–72.
21. Ebben JP, Hirsch DN, Luehmann DA, et al. Microbiologic contamination of liquid bicarbonate concentrate for hemodialysis. Trans Am Soc Artif Intern Organs. 1987;33:269–73.
22. Delin K, Attman PO, Dahlberg M. A clinical test of a new device for on-line preparation of dialysis fluid from bicarbonate powder: the Gambro BiCart. Dial Transplant. 1988;17:468–82.
23. Koda Y, Mineshima M. Advances and advantages in recent central dialysis fluid delivery system. Blood Purif. 2009;27 Suppl 1:23–7.
24. Schindler R, Beck W, Deppisch R, et al. Short bacterial DNA fragments: detection in dialysate and induction of cytokines. J Am Soc Nephrol. 2004;15:3207–14.
25. Glorieux G, Hulko M, Speidel R, et al. Looking beyond endotoxin: a comparative study of pyrogen retention by ultrafilters used for the preparation of sterile dialysis fluid. Sci Rep. 2014;4:6390.
26. Kawanishi H, Moriisha M, Sato T, et al. Fully automated dialysis system based on the central dialysis fluid delivery system. Blood Purif. 2009;27 Suppl 1:56–63.
27. Ward RA. Quality management of dialysis fluid for online convective therapies. In: Kawanishi H, Yamashita AC, editors. Hemodiafiltration – a new era, Contrib Nephrol, vol. 169. Basel: Karger; 2010. p. 1–11.

Chapter 4
Dialyzers for Hemodiafiltraion

Claudio Ronco, Sara Samoni, and Silvia De Rosa

Abstract Hemodiafiltration (HDF) is currently the most effective dialysis therapy, combining diffusion with convective transport, up to substances with a molecular weight (MW) of 50 kilo Dalton (kD). To achieve large convection volumes (>21–22 L/session), a high transmembrane pressure (TMP) is necessary. As the substitution fluid is infused after the dialyzer in postdilution HDF, which is the most frequently used HDF mode today, considerable hemoconcentration may occur within the dialyzer. Therefore, a pre-requisite to perform HDF safely and efficient is the selection of an adequate dialyzer. In this respect, both an optimal solute clearance with minimal albumin loss, excellent biocompatibility and endotoxin retaining capacity are fundamental aspects of the filter. Hence, it seems obvious that permeability should be high enough and the membrane surface area sufficiently large to achieve high convection volumes. In clinical practice, however, the magnitude of the convection volume appeared relatively independent of the dialyzers used, varying considerably in membrane surface area and length of capillaries. Hence, further research on this topic is urgently warranted.

Keywords Convection • Diffusion • End stage renal disease • Hemodialysis • Hemodiafiltration • Online hemodiafiltration • Ultrapure

Introduction

Hemodiafiltration, first introduced by Henderson in 1967, is a renal replacement technique combining diffusion and convection to enhance solute removal in a wide spectrum of molecular weights [1]. In this modality, the amount of ultrafiltration (UF) exceeds the desired fluid loss, and replacement fluid is administered to achieve

C. Ronco, MD
Department of Nephrology Dialysis and Transplantation, International Renal Research Institute (IRRIV), San Bortolo Hospital, Vicenza 36100, Italy
e-mail: cronco@goldnet.it

S. Samoni
Department of Nephrology, San Bortolo Hospital, Vicenza, Italy

S. De Rosa
International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_4

the target fluid balance. The relative contribution of convection to overall solute removal increases progressively with increasing molecular weight.

Technological developments in the fields of membranes, machines and fluids have made HDF a safe and effective technique. Synthetic membranes with reduced wall thickness allowed a combination of diffusive-convective techniques. Furthermore, the development of accurate volumetric UF control systems in dialysis machines reduced the risk for fluid balance errors. Recently, on-line preparation of sterile and pyrogen-free solutions allowed the safe infusion of large amounts of fluid, making high volume HDF a simple and safe routine procedure [2].

HDF Techniques

HDF can be performed with different techniques [3]. Classic HDF technique used an average reinfusion rate of 9 L/session in post-dilution. A blood flow over 300 ml/min was required for sufficient rates of UF at acceptable TMP gradients. The equipment included an UF control system, a reinfusion pump and a scale to weigh reinfusion bags [4]. A special form of HDF called Acetate Free Biofiltration (AFB) eliminated even small traces of acetate from both dialysate and replacement fluid inducing a significant improvement in hemodynamics of unstable patients [4]. Another variant of HDF called "High Volume HDF", used 15 L or more of reinfusion per session. The high cost of commercial replacement fluids in bags stimulated the development of a novel technique called On-line HDF. Fresh ultrapure dialysate from the dialysate inlet line is processed with multiple filtration steps and infused as replacement fluid. Large amounts of inexpensive replacement solution are generated and HDF can be performed with very high fluid turnover (up to 25–30 L/session). Fluid can be infused in either pre- or post-dilution mode, or both, in different proportions. Other techniques such as Internal Filtration HDF (iHDF), Paired Filtration Dialysis (PFD), Mid-dilution hemodiafiltration (MDHDF): Double High Flux Hemodiafiltration (DHFHDF) and Push-Pull Hemodiafiltration (PPHDF) have also been proposed to combine convection and diffusion conveniently [5–10].

Solute Removal with HDF

HDF has been shown to compare favorably with HD in terms of removal of solutes in a wide MW spectrum [11–16]. With the addition of convection, HDF enhances phosphate removal, reaching up to 30–35 mM/session [17, 18]. Controlled trials have also shown a 20–30 % reduction of β_2-microglobulin (ß2M) per session with On-line HDF, resulting in lower serum β2M levels over time [19–21]. Other large solutes which are more efficiently removed by HDF include myoglobin and retinol-binding protein [14], protein-bound solutes such as *p*-cresol [11], homocysteine [22] and leptin [23]. HDF also reduces circulating levels of advanced glycosylation end products (AGEs) which have been implicated in the pathogenesis of both

dialysis-related amyloidosis, inflammation and atherosclerosis [13]. Although several of these compounds can also be removed by hemodialysis (HD) with high flux membranes, overall, HDF is the most interesting extracorporeal technique for chronic kidney disease in this decade.

Dialyzer and Membrane Characteristics

A pre-requisite to perform HDF efficiently and safe is the selection of an adequate membrane and hemodiafilter. The diffusion process can be impaired if there is a mismatch between blood and dialysate flow distribution in the dialyzer. For this reason, it is important that central and peripheral blood and dialysate flow velocities in the filter do not differ significantly. Single fiber flow velocity should be similar in the center and the periphery of the bundle. Likewise, dialysate flow in the central region of the dialyzer and in the peripheral areas should be similar. In this way, the best blood to dialysate flow countercurrent configuration is obtained and the diffusive process is optimized. Attempts to optimize flows have been made in the blood compartment designing specific blood ports while in the dialysate compartment different options have been proposed such as space yarns (spacing filaments preventing contact between fibers) or the moiré structure (waived shape of fibers to prevent contact between adjacent fibers) [24–26].

Membrane performance, in terms of solute clearance and biocompatibility, is of paramount importance when choosing a dialyzer (Fig. 4.1). Technological advances

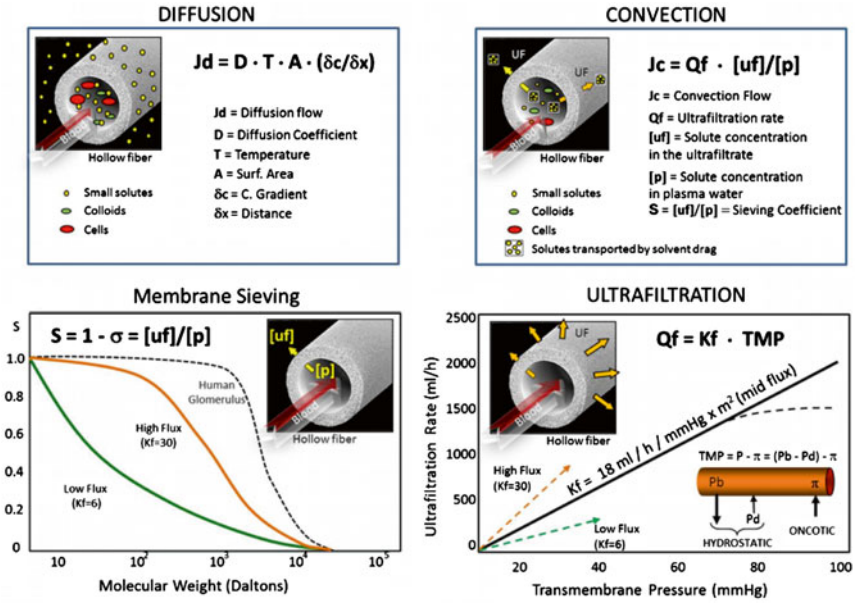


Fig. 4.1 Characteristics of different membranes in relation to mechanisms of transport

Table 4.1 Membranes divided by chemical origin and composition

Cellulosic		Synthetic		
Regenerated cellulose	Modified cellulose	Polysulfones	Polyarylethersulfones	Others
Cuprophan	CDA, DICEA	Fresenius polysulfone	PEPA	AN69 AN69ST
Cuprammonium rayon	CTA, Tricea	Helixone	Polyamix	PAN
SCE	Hemophan	Alfa polysulfone	DIAPES	PMMA
GOP DIAFIL	SMC	Toraysulfone	Arylane	EVAL
	PEG-Rc	APS		Polyamide
	Excebrane			

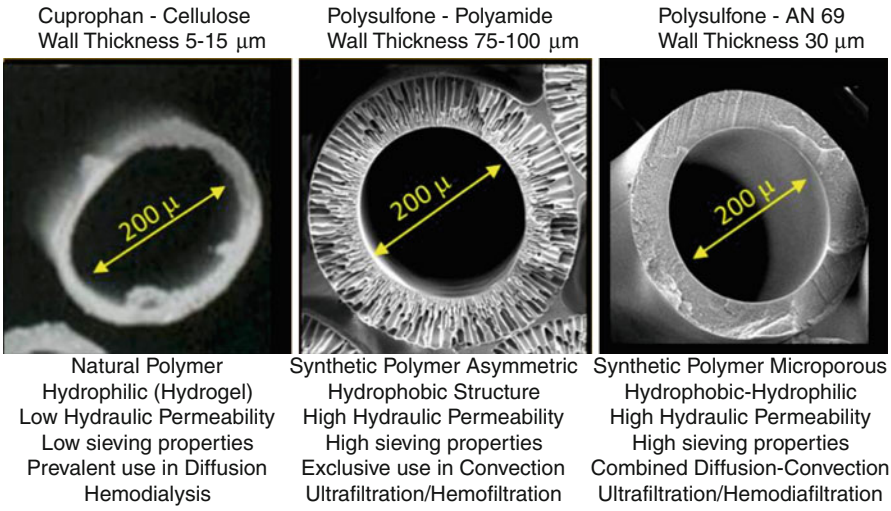


Fig. 4.2 Different membranes available on the market with different chemical composition, physical structure and performance

in membrane design, chemical composition, and sterilization methods have led to enhanced performance. The membrane and the dialyzer are the centre of the extracorporeal treatment. Thus, the choice of membrane and dialyzer among the wide selection available on the market is the key to obtain the desired blood purification for each individual clinical need. Criteria for selection may be the type of membrane, surface area, sterilization, permeability and cut-off point for molecular size.

The membrane allows to broaden the spectrum of uremic toxins that can be removed thanks to its chemical and physical characteristics. Nevertheless, the way each membrane is utilized inside a filter and the way each filter is utilized in the extracorporeal circuit can make a great deal of difference. Membranes can be divided by chemical composition as shown in the Table 4.1 (Fig. 4.2). The polymer, that composes membranes, essentially determines its chemical and physical

behavior and its possible use in the extracorporeal technique. Natural polymers derived from cellulose have progressively been substituted by synthetic polymers in which recent nano-controlled spinning techniques have contributed to enhanced performances. The ideal membrane should be biocompatible, physically strong, characterized by excellent diffusive and convective properties and by resistance to chemical and physical sterilizing agents. The optimal permeability profile should allow high sieving coefficients for large solutes with minimal or absent albumin loss. Some membranes are also characterized by high adsorption capacity and this may further contribute to solute removal properties [27]. The structure of the membrane should be thin enough to allow good diffusivity coefficients while the number and size of the pores should be standardized and optimized per unit of surface area. The inner surface of the membrane should be smooth and constructed to avoid interactions with blood components, especially platelets. Low thrombogenicity is a key feature to reduce heparin requirements and platelet activation.

The choice of the hemodiafilter should also be made according to specific criteria, such as the type of membrane and sterilization, surface area and design. The ideal filter for HDF should be highly effective regarding solute removal exhibiting constant performance over the whole treatment session. Steam or gamma sterilization avoid adverse reactions due to residuals of ethylene oxide. Today, almost all hemodiafilters are provided with hollow fiber configuration. Modern housing containing the bundle is generally light in weight and well designed to avoid dead spaces. The structure of the bundle is also important, as the number and length of fibers determine the cross section of the dialyzer and its resistance. Therefore, in each dialyzer, the size and design of the fiber bundle determine its performance. The priming volume must be as low as possible and each fiber should be surrounded by a uniform stream of dialysate during dialysis. The number of fibers and the fiber bundle density represent an important parameter to determine the filter dimension for a given surface area. To ensure a minimal activation of humoral and cellular systems of the blood, it is necessary to use a completely inert potting compound and a smooth cutting of the heads to form a smooth surface. These end surfaces are covered on both sides by end caps that contain the blood inlet and outlet ports. The composition of the potting compound has changed over the years in order to minimize risks associated with toxic compounds sometimes induced by the sterilization process, as in the case of irradiation with beta- or gamma-beams.

The main purpose of developing synthetic membranes was to create more porous membranes which could better simulate the filtration process of the natural kidney. In this way, we can improve the removal of middle MW and high MW uremic toxins (β2M). All synthetic polymers (exception for ethylenevinylalcohol copolymer – EVAL), currently on the market are hydrophobic and have to be made more hydrophilic during their production by using additives or copolymers. A new membrane called “Hydrolink” by Toray has been claimed to be less thrombogenic due to the high degree of hydrophilic surface.

Generally, the material used to make hollow fiber membranes include polysulfones, polyethersulfone, cellulose triacetate, polymethylmethacrylate, ethylenevinylalchohol, polyacrylonitrile. Nowadays, the use of poorly biocompatible unmodified cellulose dialyzer membranes is discouraged. In fact, most dialyzers are made from

synthetic polymers from the family of polysulfone/polyethersulfone. Below a short description is given of membrane materials most frequently used today.

Cellulose Triacetate: this type of membrane is characterized by a high solute permeability enabling even the removal of some ß2M by diffusion [28]. Due to the structure and thickness of the fibers, a uniform dialysate flow distribution is guaranteed. Clinical benefits include its high antithrombogenicity, an improvement in lipid metabolism and a reduction in homocysteine and AGEs [29, 30]. Since a considerable amount of albumin is adsorbed onto the membrane surface, this family of membranes offers the potential for a lower activation of the coagulation cascade than polysulfones membranes [31].

Polyacrylonitrile: this family of membranes is hydrophilic and attracts water to form a hydrogel structure that permits high diffusive and hydraulic permeability. The surface structure is able to adsorb medium-sized proteins [32]. The permeability to fluid is high and enables the removal of a broad spectrum of uremic toxins without troublesome bio-incompatibility. An interesting feature of this family is the possibility to coat the membranes with polyethylene glycol or vitamin E in order to decrease its bio-incompatibility, including leukocyte activation. Moreover, binding of heparin to the membrane surface has been shown to decrease the need for intravenous anticoagulants in case of a bleeding tendency [33, 34].

Polymethylmethacrylate: This family of membranes is characterized by high adsorptive properties due to its homogeneous structure in which the entire membrane contributes to its adsorptive capacity. This type of membrane has been shown to adsorb intact PTH and to improve pruritus [35].

Ethylenevinylalcohol: this family consists of hydrophilic and uncharged membranes with a smooth surface that retains water resulting in some protein adsorption and low blood cell activation. According to these characteristics, the long term use of EVAL membranes may reduce oxidative stress and inflammation [36, 37].

Polyamide: this family consist of asymmetric membranes with three regions. The pore size increases noticeably from the blood side to the dialysate side, being smallest at the skin layer (around 5 nm). As a consequence of this structure, complement activation and cell activation are low and oxidative stress is reduced [38, 39].

Polysulfones: these membranes have both the capacity to remove a broad range of uremic toxins and to effectively retain endotoxins [40, 41]. Thanks to their structure, these membranes provide intrinsic biocompatibility and low cytotoxicity. The elevated sieving coefficient and high hydraulic permeability promote efficient transport by convection. The original polymer can be blended with other polymers to obtain special characteristics, such as an increase in the hydrophilicity by adding polyvinylpirrolidone (PVP) [42]. Finally, significant differences among polysulfone membranes exist due to variations in both the relative amounts of co-polymers used in a particular blend and the fiber spinning process employed [43].

Polyethersulfones: the new generation of these membranes has been developed through an advanced fiber spinning process able to create a large, uniform and densely distributed pore size. Thanks to these features, the selectivity is improved [44].

As a result, polyethersulfones are characterized by an excellent middle MW removal and minimal loss of albumin. In addition, their biocompatibility features and endotoxin retaining capacity rank within the highest standards [45].

Polyarylethersulfones: this family is a combination of polysulfones and polyarylate [46]. All membranes consist of the same three-layer structure: one layer comprises the entire inner surface skin layer, a porous inner layer lies within the membrane and the third skin layer covers the outer surface. While the skin layer at the inner surface controls water and solute permeability, the outer skin blocks endotoxin transfer from the dialysate compartment to the blood. Thanks to this feature, this membrane is an excellent endotoxin filter. The amount of PVP added to the structure determines albumin losses and β2M removal.

Choice and Prescription of a Dialyzer in HDF

Theoretical Considerations

The choice of a filter for HDF depends on the selected technique. Although some techniques require a captive dialyzer, in general the selection is based on simple and clear criteria. The dialyzer should have a surface area sufficient to achieve the desired Kt/V per session and, for this purpose, a minimum filter KoA of 1000 should be prescribed (Fig. 4.3). If large filtration rates are anticipated, as is the case in high volume HDF (convection volume >20 L/session), a membrane with a minimum permeability of 30 ml/h/mmHg/m^2 should be considered. Crucial aspects, of course, are a high resistance to elevated TMP values and a low tendency to fouling and clotting. For this purpose, first, optimization of blood flow is of paramount importance. Thereafter, both Kt/V and convection volume/session should be checked carefully. If results are not satisfactory, necessary corrections should be made in treatment time and in the flow rates of dialysate and blood. When targets are still not reached after these maneuvers, another dialyzer can be selected with a different membrane or a larger surface area [47].

Sometimes, technical barriers are encountered that prevent the achievement of the desired amount of convective clearance. When TMP and end-to-end pressure drop tend to increase beyond a certain threshold in spite of blood flow optimization, a beneficial effect has been claimed of a filter flush in the predilution mode with 200 ml of saline in 30 s while the ultrafiltration pump stops (POD = Predilution On Demand). The sudden hemodilution, which is achieved with this maneuver, may induce a return of the parameters within acceptable values (Fig. 4.1) [48]. However, others were unable to show such an effect [49].

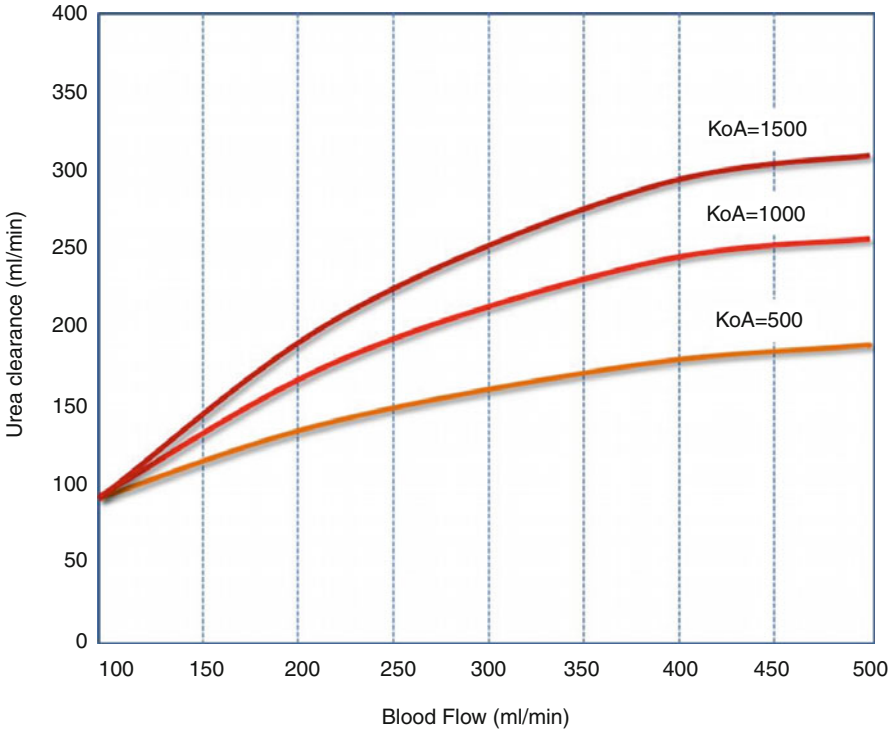


Fig. 4.3 Dialyzer clearance/blood flow domain map. Ko is the Diffusive dialysance typical for a given membrane. A is the surface area of the dialyzer

Characteristics of Dialyzers Used in Clinical Practice

As also discussed in Chap. 23, little information is available on the different dialyzers used in clinical practice. In the randomized clinical trial CONTRAST [50], comparing HDF with HD, dialyzers with a surface area between 1.7 and 2.2 m^2, an UF coefficient between 56 and 85 ml/mmHg/h, a capillary lumen diameter between 185 and 215 μm and capillary length between 225 and 280 mm were applied. Despite these dissimilar characteristics, convection volumes were rather similar. However, as these data are observational by nature and the dialyzers were clustered in participating centers, local practice patterns may have influenced these results [51]. In a cross over study in 18 HDF patients who were treated with an automatic ultracontrol technique (UltraC system), four different dialyzers were tested with constant dialysis parameters. As more or less expected, the highest convection volumes and filtration fraction were achieved by a dialyzer with the largest surface area, a high UF coefficient (75 ml/mmHg/h), a wide capillary lumen diameter (210 μm) and a capillary length of 200 mm [48]. From this study it was concluded that, although structural characteristics of dialyzers may limit their use in automatic systems,

manual settings may overcome these imperfections. At this point, it should be mentioned, however, that high convection volumes (up to 30 L) were also achieved using dialyzers with a capillary diameter of 185 μm and 1.4 m^2 surface area [52, 53]. Further research on this topic is urgently warranted.

Conclusion

A large selection of dialyzers is available on the market with different characteristics and consequently different performance features. KoA, cut-off and hydraulic permeability determine how each filter should be used and how prescription should be made. For specific techniques, captive configurations and design may be required. Based on a deep knowledge of membrane and dialyzer characteristics, the nephrologist can choose and prescribe the best device and treatment for each individual patient in relation to his clinical needs. In case of intolerance or complications, treatment parameters must be carefully checked and optimized before shifting to another device.

Teaching Points

- Hemodiafiltration is a mixed diffusive/convective therapy and requires highly permeable membranes and high performance filters.
- Filters for HDF should be defined "hemodiafilters"
- Hemodiafilters with KoA higher than 1000 should be selected to ensure enough diffusive performance
- Hemodiafilters with Kuf higher than 30 ml/h/mmHg/m^2 should be utilized
- The selection of a hemodiafilter depends on patients characteristics.
- In some cases, different options in terms of sterilization procedures, membrane composition or hemodiafilter design, may allow to personalize the device according to patient response.

References

1. Henderson LW. Biophysics of ultrafiltration and hemofiltration. In: Maher JF, editor. Replacement of renal function by dialysis. Dordrecht: Kluwer Academic; 1989. p. 300–26.
2. Ledebo I. On-line preparation of solutions for dialysis: practical aspects versus safety and regulations. J Am Soc Nephrol. 2002;13 Suppl 1:S78–83.
3. Ronco C, Cruz D. Hemodiafiltration history, technology, and clinical results. Adv Chronic Kidney Dis. 2007;14(3):231–43.
4. Maduell F. Hemodiafiltration. Hemodial Int. 2005;9(1):47–55.
5. Santoro A, Conz PA, De Cristofaro V, Acquistapace I, Gaggi R, Ferramosca E, et al. Mid-dilution: the perfect balance between convection and diffusion. Contrib Nephrol. 2005;149:107–14.
6. Pedrini LA, Cozzi G, Faranna P, Mercieri A, Ruggiero P, Zerbi S, et al. Transmembrane pressure modulation in high-volume mixed hemodiafiltration to optimize efficiency and minimize protein loss. Kidney Int. 2006;69(3):573–9.

7. Fiore GB, Guadagni G, Lupi A, Ricci Z, Ronco C. A new semiempirical mathematical model for prediction of internal filtration in hollow fiber hemodialyzers. Blood Purif. 2006;24(5–6): 555–68.
8. Miwa M, Shinzato T. Push/pull hemodiafiltration: technical aspects and clinical effectiveness. Artif Organs. 1999;23(12):1123–6.
9. Mandolfo S, Corsi A, Wratten ML, Sereni L, Imbasciati E. Evaluation of hygiene and safety controls for on-line paired hemodiafiltration (PHF). Int J Artif Organs. 2006;29(2):160–5.
10. Miller JH, von Albertini B, Gardner PW, Shinaberger JH. Technical aspects of high-flux hemodiafiltration for adequate short (under 2 hours) treatment. Trans Am Soc Artif Intern Organs. 1984;30:377–81.
11. Bammens B, Evenepoel P, Verbeke K, Vanrenterghem Y. Removal of the protein-bound solute p-cresol by convective transport: a randomized crossover study. Am J Kidney Dis. 2004; 44(2):278–85.
12. Gil C, Lucas C, Possante C, Jorge C, Gomes F, Candeias M, et al. On-line haemodiafiltration decreases serum TNFalpha levels in haemodialysis patients. Nephrol Dial Transplant. 2003; 18(2):447–8.
13. Lin CL, Huang CC, Yu CC, Yang HY, Chuang FR, Yang CW. Reduction of advanced glycation end product levels by on-line hemodiafiltration in long-term hemodialysis patients. Am J Kidney Dis. 2003;42(3):524–31.
14. Maduell F, Navarro V, Cruz MC, Torregrosa E, Garcia D, Simon V, et al. Osteocalcin and myoglobin removal in on-line hemodiafiltration versus low- and high-flux hemodialysis. Am J Kidney Dis. 2002;40(3):582–9.
15. Penne EL, van der Weerd NC, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55(1):77–87.
16. Penne EL, van der Weerd NC, Blankestijn PJ, van den Dorpel MA, Grooteman MP, Nube MJ, et al. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. Clin J Am Soc Nephrol. 2010;5(1):80–6.
17. Lornoy W, De Meester J, Becaus I, Billiouw JM, Van Malderen PA, Van Pottelberge M. Impact of convective flow on phosphorus removal in maintenance hemodialysis patients. J Ren Nutr. 2006;16(1):47–53.
18. Vaslaki L, Major L, Berta K, Karatson A, Misz M, Pethoe F, et al. On-line haemodiafiltration versus haemodialysis: stable haematocrit with less erythropoietin and improvement of other relevant blood parameters. Blood Purif. 2006;24(2):163–73.
19. Lin CL, Yang CW, Chiang CC, Chang CT, Huang CC. Long-term on-line hemodiafiltration reduces predialysis beta-2-microglobulin levels in chronic hemodialysis patients. Blood Purif. 2001;19(3):301–7.
20. Rabindranath KS, Strippoli GF, Roderick P, Wallace SA, MacLeod AM, Daly C. Comparison of hemodialysis, hemofiltration, and acetate-free biofiltration for ESRD: systematic review. Am J Kidney Dis. 2005;45(3):437–47.
21. Schiffl H. Prospective randomized cross-over long-term comparison of online haemodiafiltration and ultrapure high-flux haemodialysis. Eur J Med Res. 2007;12(1):26–33.
22. Gonella M, Calabrese G, Mengozzi A, Aleo AG, Vagelli G, Mazzotta A, et al. The achievement of normal homocysteinemia in regular extracorporeal dialysis patients. J Nephrol. 2004; 17(3):411–3.
23. Wiesholzer M, Harm F, Hauser AC, Pribasnig A, Balcke P. Inappropriately high plasma leptin levels in obese haemodialysis patients can be reduced by high flux haemodialysis and haemodiafiltration. Clin Sci (Lond). 1998;94(4):431–5.
24. Ronco C, Heifetz A, Fox K, Curtin C, Brendolan A, Gastaldon F, et al. Beta 2-microglobulin removal by synthetic dialysis membranes. Mechanisms and kinetics of the molecule. Int J Artif Organs. 1997;20(3):136–43.
25. Schneditz D, Zierler E, Jantscher A, Vanholder R, Eloot S. Internal filtration in a high-flux dialyzer quantified by mean transit time of an albumin-bound indicator. ASAIO J. 2013;59(5): 505–11.

26. Vienken J, Ronco C. New developments in hemodialyzers. Contrib Nephrol. 2001;133: 105–18.
27. Sombolos K, Tsitamidou Z, Kyriazis G, Karagianni A, Kantaropoulou M, Progia E. Clinical evaluation of four different high-flux hemodialyzers under conventional conditions in vivo. Am J Nephrol. 1997;17(5):406–12.
28. Naitoh A, Tatsuguchi T, Okada M, Ohmura T, Sakai K. Removal of beta-2-microglobulin by diffusion alone is feasible using highly permeable dialysis membranes. ASAIO Trans. 1988;34(3):630–4.
29. Van Tellingen A, Grooteman MP, Bartels PC, van Limbeek J, van Guldener C, Wee PM, et al. Long-term reduction of plasma homocysteine levels by super-flux dialyzers in hemodialysis patients. Kidney Int. 2001;59(1):342–7.
30. Sunohara T, Masuda T. Cellulose triacetate as a high-performance membrane. Contrib Nephrol. 2011;173:156–63.
31. Kuragano T, Kuno T, Takahashi Y, Yamamoto C, Nagura Y, Takahashi S, et al. Comparison of the effects of cellulose triacetate and polysulfone membrane on GPIIb/IIIa and platelet activation. Blood Purif. 2003;21(2):176–82.
32. Chanard J, Lavaud S, Randoux C, Rieu P. New insights in dialysis membrane biocompatibility: relevance of adsorption properties and heparin binding. Nephrol Dial Transplant. 2003; 18(2):252–7.
33. Lavaud S, Canivet E, Wuillai A, Maheut H, Randoux C, Bonnet JM, et al. Optimal anticoagulation strategy in haemodialysis with heparin-coated polyacrylonitrile membrane. Nephrol Dial Transplant. 2003;18(10):2097–104.
34. Frasca GM, Sagripanti S, D'Arezzo M, Oliva S, Francioso A, Mosconi G, et al. Post-dilution hemodiafiltration with a heparin-grafted polyacrylonitrile membrane. Ther Apher Dial. 2015;19(2):154–61.
35. Aucella F, Vigilante M, Gesuete A, Maruccio G, Specchio A, Gesualdo L. Uraemic itching: do polymethylmethacrylate dialysis membranes play a role? Nephrol Dial Transplant. 2007;22 Suppl 5:v8–12.
36. Sirolli V, Ballone E, Di Stante S, Amoroso L, Bonomini M. Cell activation and cellular-cellular interactions during hemodialysis: effect of dialyzer membrane. Int J Artif Organs. 2002; 25(6):529–37.
37. Matsumoto Y, Mukai M, Arihara K, Saito T, Kumagai H. Ethylene-vinyl alcohol copolymer dialyzer membrane reduces protein oxidation in hemodialysis patients. Ren Fail. 2011;33(4): 382–7.
38. Schindler R, Boenisch O, Fischer C, Frei U. Effect of the hemodialysis membrane on the inflammatory reaction in vivo. Clin Nephrol. 2000;53(6):452–9.
39. Skroeder NR, Kjellstrand P, Holmquist B, Kjellstrand CM, Jacobson SH. On complement net generation in fast hemodialysis: are high blood flow rates bioincompatible? Am J Kidney Dis. 1995;25(6):896–903.
40. Huang TF, Zhang M, Cheng LH, Zhang L, Huang M, Xu QP, et al. A novel polysulfone-based affinity membrane with high hemocompatibility: preparation and endotoxin elimination performance. Rsc Adv. 2013;3(48):25982–8.
41. Weber V, Linsberger I, Rossmanith E, Weber C, Falkenhagen D. Pyrogen transfer across high- and low-flux hemodialysis membranes. Artif Organs. 2004;28(2):210–7.
42. Hayama M, Yamamoto K, Kohori F, Sakai K. How polysulfone dialysis membranes containing polyvinylpyrrolidone achieve excellent biocompatibility? J Memb Sci. 2004;234: 41–9.
43. Bowry SK, Gatti E, Vienken J. Contribution of polysulfone membranes to the success of convective dialysis therapies. Contrib Nephrol. 2011;173:110–8.
44. Krieter DH, Morgenroth A, Barasinski A, Lemke HD, Schuster O, von Harten B, et al. Effects of a polyelectrolyte additive on the selective dialysis membrane permeability for low-molecular-weight proteins. Nephrol Dial Transplant. 2007;22(2):491–9.
45. Krieter DH, Lemke HD. Polyethersulfone as a high-performance membrane. Contrib Nephrol. 2011;173:130–6.

46. Hoenich NA, Katopodis KP. Clinical characterization of a new polymeric membrane for use in renal replacement therapy. Biomaterials. 2002;23(18):3853–8.
47. Chapdelaine I, de Roij van Zuijdewijn CL, Mostovaya IM, Levesque R, Davenport A, Blankestijn PJ, et al. Optimization of the convection volume in online post-dilution haemodiafiltration: practical and technical issues. Clin Kidney J. 2015;8(2):191–8.
48. Albalate RM, Perez GR, de Sequera OP, Alcazar AR, Corchete PE, Puerta CM, et al. Clinical application of Ultracontrol(R): infusion volume and use with different dialyzers. Nefrologia. 2011;31(6):683–9.
49. Zimbudzi E. Intermittent saline flushes or continuous saline infusion: what works better when heparin-free dialysis is recommended? Int J Nephrol Renov Dis. 2013;6:65–9.
50. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.
51. Chapdelaine I, Mostovaya IM, Blankestijn PJ, Bots ML, van den Dorpel MA, Levesque R, et al. Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration. Blood Purif. 2014;37(3):229–37.
52. Maduell F, Rodriguez N, Sahdala L, Coronel D, Arias GM, Ojeda R, et al. Impact of the 5008 monitor software update on total convective volume. Nefrologia. 2014;34(5):599–604.
53. Maduell F, Arias-Guillen M, Fontsere N, Ojeda R, Rico N, Vera M, et al. Elimination of large uremic toxins by a dialyzer specifically designed for high-volume convective therapies. Blood Purif. 2014;37(2):125–30.

Part II
Hemodiafiltration Equipment

Chapter 5
Baxter Online Hemodiafiltration Systems

Jan Sternby, Anders Felding, and Lars-Göran Nilsson

Abstract The interest in convection as a transport principle in haemodialysis grew in the 1970s. In 1980 Gambro launched the world's first complete system for auto-controlled haemofiltration, AK-10 HFM 10-1, an important breakthrough in improving clearance of middle sized molecules. Bags with pharmacy-prepared infusion fluid were used and fluid balance was achieved by weighing devices. An experimentally modified HFM-10 system was found to safely deliver on-line prepared fluid for convective treatments.

The GHS-10 system, released in 1985, was the first complete system for haemofiltration treatments with continuous, on-line preparation of substitution fluid, incorporating efficient pyrogen-retaining ultrafilters. The cost of the fluid was much reduced and the need to carry fluid bags was eliminated. This system was a forerunner of the on-line machines that are available today. It was followed in 1987 by the MPS-10 Multi Purpose System, which also allowed performing the "hybrid treatment" of haemodiafiltration (HDF). In the early 1990s came a new system design in the AK 100 ULTRA machine, later followed by the AK 200 ULTRA and the AK 200 ULTRA S dialysis systems, the latter still widely used for on-line HDF treatments. More recently the ARTIS and ARTIS PHYSIO systems were introduced with innovative technologies to improve usability in HD and HDF treatments.

Keywords ARTIS PHYSIO • Disinfection • Online hemodiafiltration • Predilution • Postdilution • Substitution fluid • Transmembrane pressure • UltraControl

J. Sternby, PhD
Department of R&D, Treatment Systems Research,
Gambro Lundia AB, a Subsidiary of Baxter International, Inc., Lund, Sweden

A. Felding, MScEE
Technical Services, System Support,
Gambro Lundia AB, a Subsidiary of Baxter International, Inc., Lund, Sweden

L.-G. Nilsson, BSc (✉)
Baxter CSO, Renal Therapeutic Area,
Gambro Lundia AB, a Subsidiary of Baxter International, Inc.,
P.O.Box 10101, Lund SE-22010, Sweden
e-mail: lars_goran_nilsson@baxter.com

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_5

Introduction

The interest in convection as a transport principle in haemodialysis grew in the 1970s. In 1980 Gambro launched the world's first complete system for auto-controlled haemofiltration, AK-10 HFM 10-1, an important breakthrough in improving clearance of middle sized molecules. Bags with pharmacy-prepared infusion fluid were used and fluid balance was achieved by weighing devices. An experimentally modified HFM-10 system was found to safely deliver on-line prepared fluid for convective treatments [1].

The GHS-10 system, released in 1985, was the first complete system for haemofiltration treatments with continuous, on-line preparation of substitution fluid, incorporating efficient pyrogen-retaining ultrafilters. The cost of the fluid was much reduced and the need to carry fluid bags was eliminated. This system was a forerunner of the on-line machines that are available today. It was followed in 1987 by the MPS-10 Multi Purpose System, which also allowed performing the "hybrid treatment" of haemodiafiltration (HDF). In the early 1990s came a new system design in the AK 100 ULTRA machine, later followed by the AK 200 ULTRA and the AK 200 ULTRA S dialysis systems, the latter still widely used for on-line HDF treatments. More recently the ARTIS and ARTIS PHYSIO systems were introduced with innovative technologies to improve usability in HD and HDF treatments, see Fig. 5.1.

Water Treatment System

A water treatment system for hemodialysis shall be designed on knowledge of the feed water characteristics. This system should ensure a water quality at the dialysis machine inlet complying to applicable national standards, as well as the international ISO 13959 standard (Water for haemodialysis and related therapies). Concentrates must meet the requirements of ISO 13958 (Concentrates for haemodialysis and related therapies), and the produced dialysis fluid those of the ISO 11663 standard (Quality of dialysis fluid for haemodialysis and related therapies).

Short Description and Outline of the HDF Machine

ULTRA on-line systems by Gambro have long been used for HDF and HF treatments [2]. Substitution fluid with a high sterility assurance level is prepared in a final filtration step using a sterile single-use filter device, from which a sterile line takes the fluid directly to the point of mixing with blood. Two stationary

Fig. 5.1 ARTIS dialysis system

ultrafilters are located upstream in the system; the first acts on the incoming dialysis water to ensure a minimal microbial bioburden on the machine's internal lines and the second removes microbial products deriving from the concentrates. Each of the filters employed by the fluid preparation system shows a substantial reduction capacity for endotoxin. As result the system effectively converts standard dialysis water and concentrates to a fluid that can be used without risk of pyrogenic reactions.

By extracting the substitution fluid from the patient side of the UF measuring system the fluid balance accuracy is unaffected by the accuracy of the substitution fluid flow rate. Technical features of the ARTIS PHYSIO dialysis machine are summarized in Table 5.1.

Table 5.1 Techical features of the Artis Physio™ dialysis machine

Technical features	ARTIS PHYSIO (Baxter)
Blood pump flow range (ml/min)	10–500 ml/min
Dialysate flow (ml/min)	300–800 ml/min
Dialysate flow selection mode	Presettable flow rate; adjustment proposed by the machine in HDF mode based on substitution flow rate
Emergency button	Yes, stop treatment button and UF stop independently from other functions
Substitution mode: manual/automatic	Automated UltraControl modality (postdilution), or manual pressure control (postdilution), or manual volume control (post- and predilution)
Settable parameter(s) in volume control mode	Substitution fluid flow rate in ml/min (volume automatically calculated and shown)
Substitution fluid flow range	20–450 ml/min (1.2–27 L/h)
Electrolyte concentration adjustment	Na^+ 130–160 mmol/l, HCO_3^- 24–38 mmol/l, other electrolytes based on concentrate selection
Substitution fluid delivery options	postdilution, predilution
Online priming, rinsing, IV bolus	Yes
Stationary ultrafilters	Yes, 2 U 9000 ultrafilters
Additional ultrafilter	Yes
Integrity pressure test ultrafilter	Final single-use filter is integrity tested in production
Blood access monitoring	Yes, arterial and venous pressure
Online clearance monitoring	Yes (DIASCAN)
Blood volume monitoring (BVM)	Yes (HEMOSCAN)
Blood temperature monitoring	No
Other monitoring options	Plasma conductivity and ionic mass balance
	Blood pressure monitoring
	Optional pH meter
Alarm and information signals	Alarms: auditory and visual, intensity by priority level. Information signals: notifications, Smartscan messages
IT connectivity	10/100 based T Ethernet port, RS232 serial port, UAB port. Proprietary data exchange protocol and HL7 compatible protocol
Data transfer via patient card	Yes (contactless device)
Standard safety features	According to ICE 60601-1-1, IEC 60601-2-16, and other applicable standards
Advanced safety features	Biofeedback system reduces the risk for excessive hemoconcentration in postdilution high volume HDF
Touchscreen operation and ergonomic design	Yes
Special features	Screen navigation through five-button NAVPAD interface

HDF Prescription Principles (Manual/Automatic)

Different methods can be used to control the substitution fluid flow rate. In pressure control the transmembrane pressure (TMP) is kept constant at a value chosen at the beginning of the treatment. Maintaining the optimal pressure difference

will in theory maximize the total convection but it is not possible to prescribe a certain volume (and thus treatment dose) to be achieved within a given treatment time.

In volume control the total convective volume is prescribed with the substitution fluid flow rate held constant over the prescribed treatment time. The disadvantage with volume control, particularly in postdilution HDF, is that it is difficult to estimate in advance how high flow rate can be achieved and to what extent the TMP rises during the treatment due to haemoconcentration. Machine alarms during treatment are common as TMP becomes too high in relation to the set alarm limits.

In contemporary on-line HDF machine systems by Baxter the manual pressure control function for postdilution has been replaced by the automated UltraControl modality. When activated at treatment start the UltraControl mode automatically tests for the optimal TMP level. Here the TMP is increased in steps with the ultrafiltration rate being monitored for each TMP level. This TMP scan continues until the increase in ultrafiltration rate becomes insignificant, when the scan is aborted and the system automatically moves into a pressure control mode using the optimal TMP result of the scan. Additional TMP scans are performed during the treatment to account for changes in rheological conditions. Use of the UltraControl modality has been found to make postdilution HDF delivery simpler and more effective by achieving greater convective volume with fewer haemoconcentration-related machine alarms [3, 4]. For snapshots of the screen, see Figs. 5.2 and 5.3.

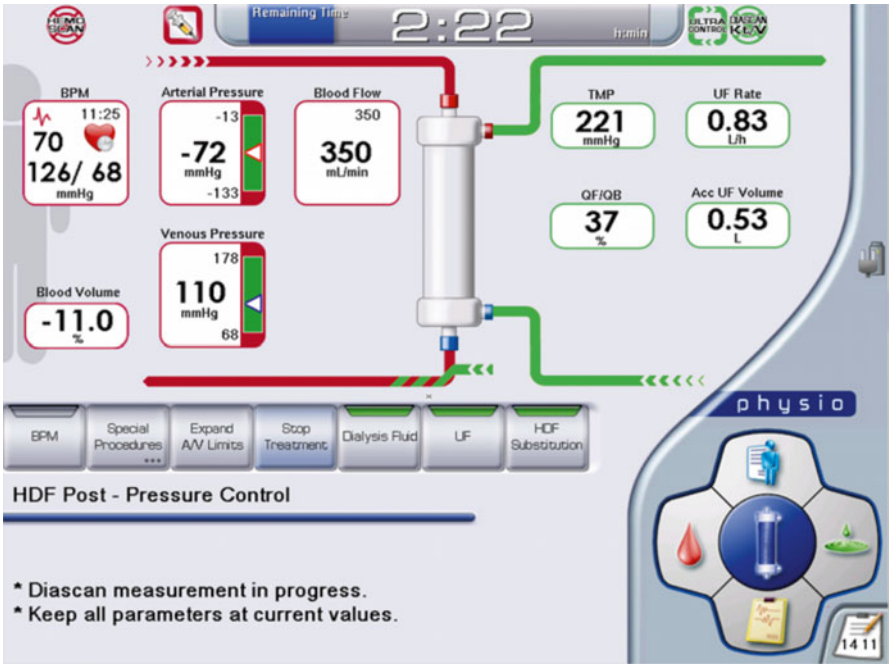


Fig. 5.2 Snapshot of screen I

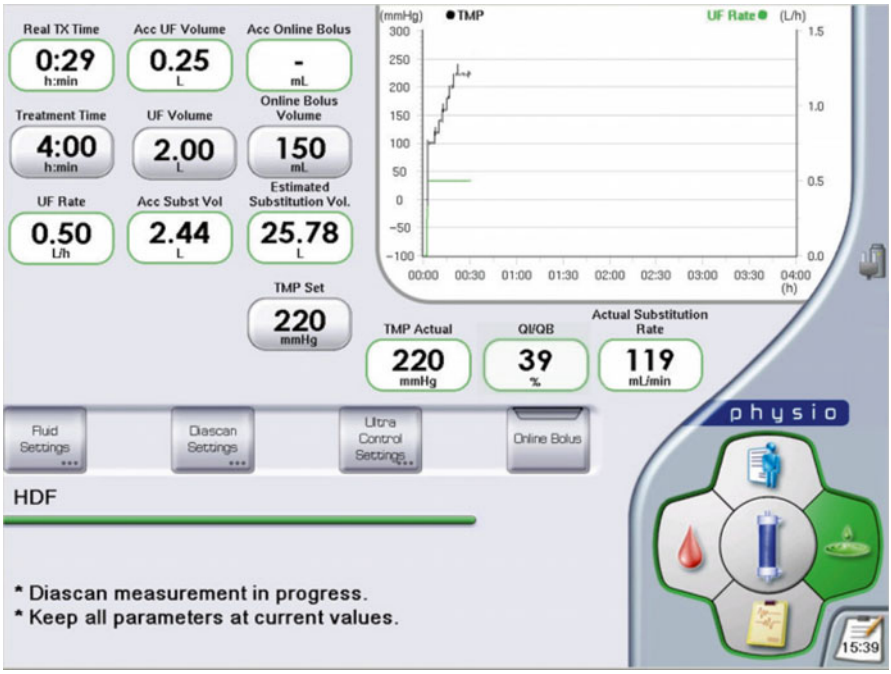


Fig. 5.3 Snapshot of screen II

HDF Modalities

The ARTIS PHYSIO dialysis system allows for on-line HDF to be delivered in post-dilution or in pre-dilution mode. The post-dilution mode offers best possible blood purification [5].

Specificities of the Disposables Required

Any high-flux dialyser with standard connections can be used; a hollow-fibre inner diameter greater than 200 µm and an open membrane wall structure facilitate achieving large convective flow rates. The membrane permeability profile should be such that excessive albumin loss is avoided.
The bicarbonate concentrate shall be of the dry BiCart cartridge type.

Additional Therapeutic Options

The ARTIS dialysis systems allow for:

- Citrate dialysis fluid (100 % acetate-free) to be used for on-line HDF [6].

Additional Monitoring Options

The ARTIS on-line HDF systems incorporate:

- Ionic dialysance (DIASCAN)
- Relative blood volume monitoring (HEMOSCAN).

Cleaning and Disinfection

The ARTIS dialysis system provides several methods to clean and disinfect its internal circuit (see Operator's Manual). A recommended procedure is disinfection by heat between treatments and by heat plus citric acid (CleanCart C) after the last treatment of the day. When a Gambro CWP water treatment system is used the machine disinfection can be integrated with the hot water flushing of the water distribution loop.

For overnight or weekend storage the ARTIS dialysis system offers the option of using a bacteriostatic level of disinfectant to protect the hydraulic circuit from microbial contamination.

Risk Management System

Risk management principles are the same for on-line HDF and HD. For HDF the clear borderline in the fluid path between disinfected area upstream and sterile area downstream of the final sterile filter membrane ensures the appropriate substitution fluid quality.

Display of Settings and Connection to Hospital Information System

Not specific for HDF; various solutions available through Baxter local representatives.

Cost Assessment

Changing from conventional HD to on-line HDF treatments is associated with some additional costs. An elaborate quality management system is required for on-line HDF delivery [7]. Dialysis water testing may have to be increased above what is required for HD. Access surveillance may need to be intensified as on-line HDF needs a high blood flow rate to achieve an effective convective volume.

Future Directions

When on-line HDF is used as means to optimise middle molecule removal it is best performed in postdilution mode with a high exchange volume. In all cases the high-flux membrane's pore size distribution limits what solute sizes are removed. New dialysis membranes for HD are currently being developed and initial in vitro data indicate that dialysers with such membranes can in HD provide similar or superior large solute clearances to conventional high-flux dialysers in on-line HDF [8]. Clinical trials are ongoing to confirm these preliminary results.

Acknowledgement AK 100 Ultra, AK 200 Ultra, Artis, BiCart, CleanCart, Diascan, Hemoscan, MCO, NavPad and U 9000 are trademarks of Baxter International Inc. or its affiliates.

References

1. Shaldon S, Beau MC, Deschodt G, et al. Three years of experience with on-line preparation of sterile pyrogen-free infusate for haemofiltration. Contrib Nephrol. 1982;32:161–4.
2. Ledebo I. On-line preparation of solutions for dialysis: practical aspects versus safety and regulations. J Am Soc Nephrol. 2002;13 Suppl 1:S78–83.
3. Teatini U, Steckiph D, Romei Longhena G. Evaluation of a new online hemodiafiltration mode with automated pressure control of convection. Blood Purif. 2011;31:259–67.
4. Panichi V, De Ferrari G, Saffioti S, et al. Divert to ULTRA: differences in infused volumes and clearance in two on-line hemodiafiltration treatments. Int J Artif Organs. 2012;35:435–43.
5. Meert N, Eloot S, Waterloos MA, et al. Effective removal of protein-bound uraemic solutes by different convective strategies: a prospective trial. Nephrol Dial Transplant. 2009;24:562–70.
6. Molina Nuñez M, de Alarcón R, Roca S, et al. Citrate versus acetate-based dialysate in on-line haemodiafiltration. A prospective cross-over study. Blood Purif. 2015;39:181–7.
7. Ward R. Basics for delivering safe and effective HDF. Presentation at the ERA-EDTA 2014 Congress: EuDial symposium. http://www.era-edta.org/eraedta2013/ematerial/180513/cme3.1/Ward/index.html.
8. Boschetti-de-Fierro A, Voigt M, Hulko M, et al. MCO dialyzers: enhanced selectivity high-flux. World Congress of Nephrology; Abstract SAT-481.

Chapter 6
Dialog+: B. Braun Hemodiafiltration System

Marten Kelm, Björn Bröker, and Claudia Barth

Abstract B.Braun provides renal care with all modalities of dialysis for >23,000 patients in 24 countries. The hemodialysis system Dialog + was introduced to the market in 2003. It is available in different configurations, e.g. single-pump, double-pump and HDF-online. All machines are suitable for hospital and in-center dialysis.

In the HDF-online machine, the online production of ultra-clean dialysate for autopriming in hemodialysis and for substitution fluid in HF/HDF treatments is performed by a two-stage dialysis fluid filter system to ensure the ultra-pureness of the substitution solution.

Keywords Dialog • Dialyser inlet pressure • Disinfection • Online hemodiafiltration • Predilution • Postdilution • Substitution fluid • Transmembrane pressure

Introduction

B.Braun provides renal care with all modalities of dialysis for >23,000 patients in 24 countries. The hemodialysis system Dialog+ was introduced to the market in 2003. It is available in different configurations, e.g. single-pump, double-pump and HDF-online. All machines are suitable for hospital and in-center dialysis.

In the HDF-online machine, the online production of ultra-clean dialysate for autopriming in hemodialysis and for substitution fluid in HF/HDF treatments is performed by a two-stage dialysis fluid filter system to ensure the ultra-pureness of the substitution solution, see Fig. 6.1

M. Kelm, MBA • C. Barth, MD (✉)
Department of Medical Scientific Affairs, B. Braun Avitum AG, Melsungen, Germany
e-mail: claudia.barth@bbraun.com

B. Bröker
Department of Research and Development, B. Braun Avitum AG, Melsungen, Germany

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_6

Fig. 6.1 Dialog+ HDF-machine

Water Treatment System

A water treatment system for hemodialysis shall be designed on knowledge of the feed water characteristics. This system should ensure a water quality at the dialysis machine inlet complying to applicable national standards, as well as the international ISO 13959 standard (Water for haemodialysis and related therapies). Concentrates must meet the requirements of ISO 13958 (Concentrates for

haemodialysis and related therapies), and the produced dialysis fluid those of the ISO 11663 standard (Quality of dialysis fluid for haemodialysis and related therapies).

Short Description and Outline of the HDF Machine

The purified water from the RO system enters the machine via a pressure reducer. Degassing of the water is required to improve the treatment and is performed by a degassing pump and chamber. In parallel, the water is heated to a set temperature (usually 37 °C). The water is then collected in a tank ready to be mixed in the dialysate preparation system.

Processed water is mixed with bicarbonate and acid concentrate conductivity controlled. Bicarbonate powder or central concentrate supply can be used optionally. Substitution fluid is produced online from dialysis fluid. The fresh dialysis fluid passes the first ultrafilter and enters the dialysis circuit, whereas the substitution fluid passes a second ultrafilter before it reaches the patient. In HDF treatment mode, the substitution flow (Qs) is split from the dialysate flow (Qd). Thus the dialysate effectively reaching the dialyser is reduced. This is compensated by automatically setting the dialysate flow to 600 ml/min in case HDF is activated, but can be changed according to the physician's prescription.

Fluid balance is ensured by the balance chamber of the machine, consisting of two chambers separated by a flexible membrane allowing to be filled from one side, while an identical volume is emptied from the other side.

The membrane has a magnetic sensor determining the exact membrane position and thereby controlling the dialyzing fluid flow, thus ensuring continuity in the flow of the dialysate. Ultrafiltration removal is carried out by the UF pump which bypasses the balancing chambers.

Technical features of the Dialog+ dialysis machine are summarized in Table 6.1.

HDF Prescription Modality (Manual/Automatic)

Treatment time, net ultrafiltration (UF) and blood flow rate are usually prescribed parameters.

The machine principle is based on volume control, which means that either substitution rate/min or total substitution target volume can be set. The filtration fraction (FF) is calculated and displayed as the ratio between the total UF rate (net UF plus substitution flow rate) and the blood flow rate. Any parameter change immediately adapts the ratio according to the new settings. Individual alarm limits, which can be set in the system configuration mode, monitor the FF within the allowed alarm limit ranges.

Table 6.1 Technical features of the dialog + dialysis machine

Technical features	Dialog+ (B. Braun)
Blood pump flow range (ml/min)	50–600 ml/min
Dialysate flow (ml/min)	300–800 ml/min
Dialysate flow selection mode	Flow profiles in addition to manual setting (free and predefined)
Emergency button	No full automatic button, necessary functions available on main screen
Substitution mode: manual/automatic	Manual setting
Settable parameter(s) in volume control mode	Substitution flow rate (ml/min); substitution volume (L); display of filtration fraction (%) with configurable alarm and warning limits
Substitution fluid flow range	20–400 ml/min
Electrolyte concentration adjustment	Profiles in additions to manual setting
Substitution fluid delivery options	Predilution, postdilution
Online priming, rinsing, IV bolus	Yes
Stationary ultrafilters	Yes, 2, Diacap Ultra
Additional ultrafilter	No additional filter in disposable
Integrity pressure test ultrafilter	Yes
Blood access monitoring	Arterial and venous pressure
Online clearance monitoring	Yes (Adimea)
Blood volume monitoring (BVM)	Not available
Blood temperature monitoring	Not available. Dialysing temperature profiles available
Other monitoring options	Blood pressure measurement (ABPM), Kt/V-monitoring based on measurement of removed uremic substances (Adimea), monitoring of clotting via dialyser inlet pressure
Alarm and information signals	Acoustical and optical alarms and warnings, help function – text display
IT connectivity	Unidirectional (BSL, bed side link), or bidirectional (Nexadia) data transfer and monitoring system between dialysis machine and IT equipment
Data transfer via patient card	Yes
Standard safety features	Complying to international standards
Advanced safety features	Warning for ratio blood flow versus UF rate (FF), dynamic arterial and venous pressure window
Touchscreen operation and ergonomic design	Yes
Special features	Biologic RR comfort: biofeedback system for reduction of hypotensive episodes

HDF Modalities

The Dialog+ system offers the possibility to run HDF treatments either in pre- or post-dilution mode. A change of modes during the treatment is possible but requires a blood pump stop, manual handling and an additional blood tubing accessory for the predilution mode. Screen snapshots are shown in Figs. 6.2 and 6.3.

Specificities of Disposables Required

Hemodiafilters: It is essential that the choice of the dialyser should match the high ultrafiltration volumes of HDF treatment. Therefore a large surface area and a high UF-coefficient (KUF) are needed. High-flux dialyser are recommended in order to keep the transmembrane pressure (TMP) within the allowed range (depending on the substitution flow rate). Since high TMP pressures are common in HDF, a filter with the lowest loss of albumin per session is a preferred choice.

Blood tubing set: B.Braun offers a blood tubing set (HDF-online tubing kit) especially for HDF-online treatments. Standard blood tubing sets together with an additional substitution line can alternatively be used to perform HDF-online treatments.

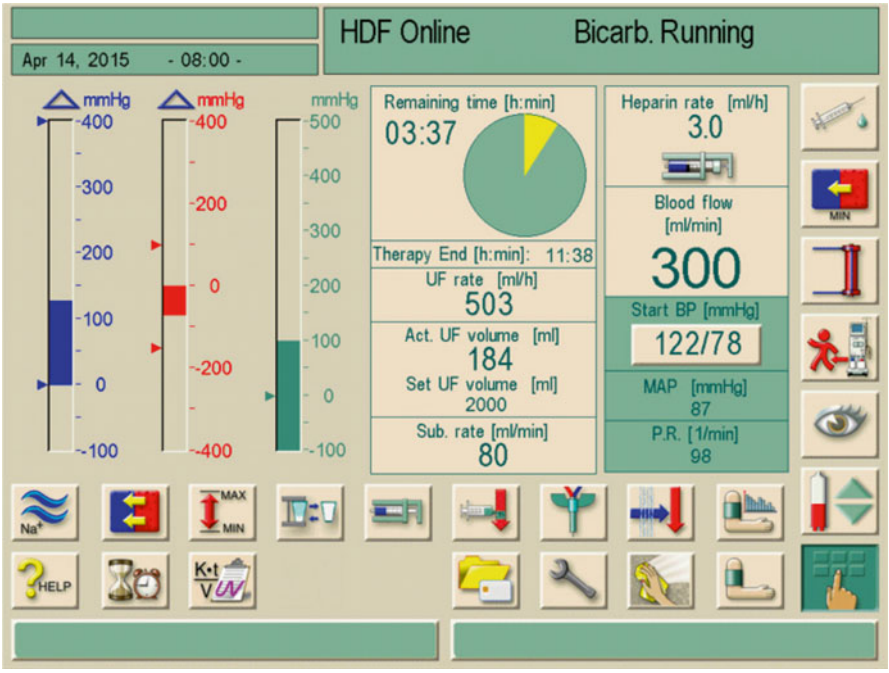


Fig. 6.2 Snapshot screen I

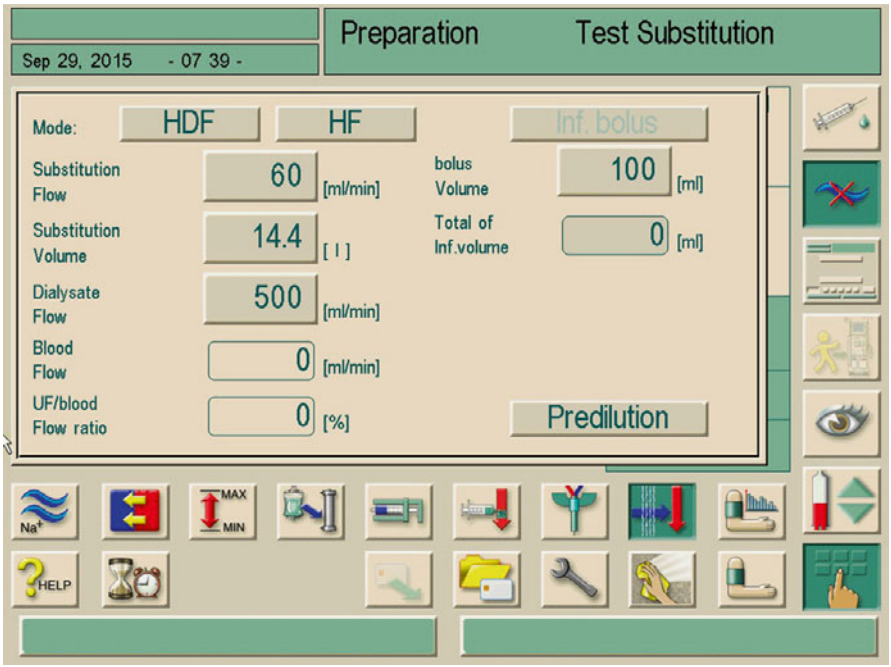


Fig. 6.3 Snapshot screen II

Ultrafilters: The B.Braun Dialog+ system uses two dedicated polysulfone-based ultrafilters (Diacap Ultra) for HDF and HF therapies. The ultrafilters are characterized by long exchange intervals (150 therapies or 900 h of treatment time).

Additional Therapeutic Options

Dialog+ offers to set profiles for particular function parameters such as:

- Dialysate conductivity
- Bicarbonate conductivity
- Dialysate flow
- Dialysate temperature
- Ultrafiltration
- Heparin

Profiles can be combined and set individually.

Additional Monitoring Options

The Dialog+ system offers the following additional monitoring options:

- BioLogic RR Comfort: The biologic RR Comfort option is an automatic blood pressure stabilization system for the prevention of hypotensive episodes. This

system uses actual blood pressure values as well as patient specific blood pressure progressions from past treatments to adjust the UF-control of the machine [1].
- Adimea: A device for continuous monitoring of the delivered dialysis dose (Kt/V). The device uses UV-absorbance measurement to assess the reduction of urinary waste products in the dialysate outlet of the dialysis machine. Due to continuously recorded measurements the Kt/V and the urea reduction ratio (URR) can be determined and displayed online. It can be applied in HD as well as HDF treatments [2].

Cleaning and Disinfection

Disinfection of the machine should be performed to reduce to minimum the bacterial level. Dialog+ offers three types of disinfection:

1. Chemical disinfection
2. Thermal disinfection
3. Citro-thermal disinfection

During disinfection the disinfectant reaches all parts of the hydraulic circuit. Temperature and duration of disinfection depend on the disinfectant used. After the disinfection phase a rinsing phase removes any residual disinfectant. The machine performs the disinfection/rinsing phase automatically. Disinfection cycles can be programmed to be performed automatically.

Risk Management System

Additional to the safety features required by international standards, the system offers the following:

– Warning for too high ratio blood flow rate versus UF-rate (filtration fraction; essential to avoid excess hemoconcentration in post-dilution mode)
– Monitoring of blood side dialyser inlet pressure as an indicator for secondary membrane built-up or clotting
– Dynamic adjustment of alarm limits for arterial- and venous pressures (PA and PV)

Display of Settings and Connection to Hospital Information System

Connectivity to internet and/or hospital information system: B.Braun offers the Nexadia system for bidirectional connection to a central database. With Nexadia, individual settings for the dialysis treatment are automatically transferred to the dialysis machine. In the other direction, Nexadia automatically collects all relevant treatment and patient data from the machine. A unidirectional interface of the Dialog+ systems to several databases is possible. Patient therapy prescription is supported by using the patient card.

Cost Assessment

Recent prospective trials suggest that on-line hemodiafiltration (HDF) improves survival, if high convective volumes are reached [3–5]. However, these results await confirmation. In general, HDF treatments are characterized by slightly higher costs mainly due to extra disposable costs and higher water consumption. Higher costs might be compensated when considering patient quality of life or reduced EPO usage [6]. Further studies are necessary to answer this question.

References

1. Mancini E, Mambelli E, Irpinia M, et al. Prevention of dialysis hypotension episodes using fuzzy logic control system. Nephrol Dial Transplant. 2007;22:1420–7.
2. Castellarnau A, Werner M, Günthner R, Jakob M. Real-time Kt/V determination by ultraviolet absorbance in spent dialysate: technique validation. Kidney Int. 2010;78:920–5.
3. Maduell F, Moreso F, Pons M, et al.; for the ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
4. Grooteman MP, van den Dorpel MA, Bots ML, et al.; for the CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
5. Ok E, Asci G, Toz H, Ok ES, et al.; for the Turkish Online Haemodiafiltration Study. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF study. Nephrol Dial Transplant. 2013;28:192–202.
6. Mazairac AH, Blankestijn PJ, Grooteman MP, et al.; for the CONTRAST Investigators. The cost-utility of haemodiafiltration versus haemodialysis in the convective transport study. Nephrol Dial Transplant. 2013;28:1865–73.

Chapter 7
Online Hemodiafiltration Systems by Bellco: Flexya

Andrea Fiorenzi

Abstract Flexya Hemodiafiltration System is a monitor equipped with a triple peristaltic pump, employing several disposable extracorporeal circulation kits, functioning on a single cassette system. The kits can be used for different types of treatments.

The Flexya double-stage dialysis fluid preparation system uses either bags with bicarbonate powder and acid concentrates, or concentrate solutions from the hospital's centralized system. The system features an ultrafilter on the inlet water and a double dialysis fluid filtration system to provide ultrapure substitution fluid for online treatments. Dialysis progress, dose, and patient monitoring are controlled by several sensors to prevent potential complications.

Keywords Disinfection • Endogenous infusion • Online hemodiafiltration • Predilution • Postdilution • Single pass circuit • Substitution fluid • Transmembrane pressure

Introduction

Flexya Hemodiafiltration System is a monitor equipped with a triple peristaltic pump, employing several disposable extracorporeal circulation kits, functioning on a single *cassette system*. The kits can be used for different types of treatments.

The *Flexya* double-stage dialysis fluid preparation system uses either bags with bicarbonate powder and acid concentrates, or concentrate solutions from the hospital's centralized system. The system features an ultrafilter on the inlet water and a double dialysis fluid filtration system to provide ultrapure substitution fluid for online treatments. Dialysis progress, dose, and patient monitoring are controlled by several sensors to prevent potential complications.

A. Fiorenzi, MBA
Equipment Operations, Bellco Srl, Via Camurana, 1, Mirandola 41037, Italy
e-mail: andrea.fiorenzi@bellco.net

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_7

Water Treatment System Required

The water treatment system for hemodialysis and hemodiafiltration shall be designed on knowledge of the feed water characteristics. This system should ensure a water quality at the dialysis machine inlet complying to applicable national standards, as well as the international ISO 13959 standard (Water for haemodialysis and related therapies). Concentrates must meet the requirements of ISO 13958 (Concentrates for haemodialysis and related therapies), and the produced dialysis fluid those of the ISO 11663 standard (Quality of dialysis fluid for haemodialysis and related therapies).

Short Description and Outline of the HDF Machine

Single pass: water flows at a high flow rate, one direction, thus washing away impurity and chemical residues during disinfections. Connections between monitor and disposable tubing sets, reduced in number by the cassette system, are integrated in the disinfection process of the machine. With luer lock connections, disposable installation can be performed without contaminating connections and infusion lines.

Dialysis fluid and substitution fluid: The dialysis and substitution fluid do not differ, facilitating procedures during extracorporeal circuit priming, without the necessity of physiological solution bags.

Technical aspects of fluid balance: extract substitution fluid from the dialysis fluid, in such a way that the dialysis fluid flow rate is kept at its prescribed value. Another feature unique to *Flexya* safety is the independency of the weight loss system from the amount of substitution volume: the *differential flow meter* system measures the difference between the fluid prepared by the monitor (independent if to the dialyzer or substitution port) and the fluid returned from the dialyzer. Technical features of the Flexya dialysis machine are summarized in Table 7.1.

HDF Prescription Modality (Manual/Automatic)

Flow rate can be set at a fixed value by separately setting the amount infused in pre- and in post-dilution, or automatically by the so-called *Auto Qinf System*: a program to maximize the substitution volume, optimizing dialyzer performances, controlling transmembrane pressure at a specific (adjustable) value; constraints are maximum and minimum rate for pre- and postdilution flows and filtration fraction. Hematocrit measures (with Hemox) are used to calculate filtration fraction; when these are not available, postdilution substitution flow rate is kept below 29 % of blood flow rate.

Table 7.1 Technical features of the Flexya dialysis machine

Technical features	Flexya (Bellco)
Blood pump flow range (ml/min)	30–700 ml/min
Dialysate flow (ml/min)	300–1500 ml/min
Dialysate flow selection mode	Manual setting
Emergency button	Hardware buttons stopping blood and dialysate flows; knob to reduce and stop blood flow; software button to automatically minimize weight loss, infuse a solution bolus and start pressure measures
Substitution mode: manual/ automatic	Manual (on choice) or automatic (autoQinf)
Settable parameter(s) in volume control mode	Pre and post dilution infusion flow rate, transmembrane pressure threshold
Substitution fluid flow range	Up to 400 ml/min (24 l/h)
Electrolyte concentration adjustment	Via two conductivity settings, via conductivity profiles, authomatically via Aequilibrium
Substitution fluid delivery options	Predilution, postdilution, pre + postdilution, middilution, endogenous reinfusion
Online priming, rinsing, IV bolus	Yes
Stationary ultrafilters	2, dailyclean and H2OClean
Additional ultrafilter	Yes
Integrity pressure test ultrafilter	Before each treatment
Blood access monitoring	Fistula and venous pressure
Online clearance monitoring	Via conductivity step method
Blood volume monitoring (BVM)	Via hematocrit measures
Blood temperature monitoring	Via optical measures on blood lines
Other monitoring options	Plasma sodium concentration (Natrium sensor), oxygen saturation
Alarm and information signals	A four color lamp on the top and a buzzer signal alarm conditions; colored alarm windows and messages displayed on the screen
IT connectivity	Yes, via Ethernet port
Data transfer via patient card	Yes, via RFiD data transmission
Standard safety features	In compliance with international standards
Advanced safety features	Automatic transmembrane pressure control; pre dialyzer, pre and post infusion pressure alarms
Touchscreen operation and ergonomic design	Touchscreen display settable at two different heights and adjustable by small rotation
Special features	Warning for potential hypotensive episodes (Soglia, using oxygen saturation)

HDF Modalities

The *Flexya* system (Fig. 7.1) implements several hemodiafiltration treatments:

- Substitution fluid can be infused in predilution and postdilution mode, or both simultaneously (mixed dilution).

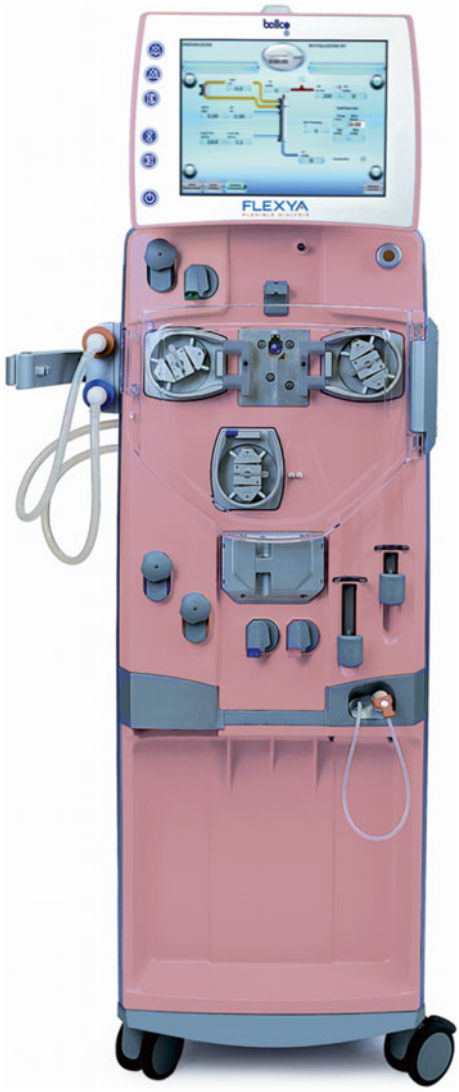


Fig. 7.1 Flexya HDF-machine

- Mid-dilution HDF [1, 2]: substitution fluid is infused in post-dilution for the first part of blood flow path and in pre-dilution for the second. The same dialysis fluid flows against and with the current, respectively with the two blood flow paths.
- HFR [3, 4] and SUPRA [5]. A pump extracts untreated plasma water from the first chamber of the dialyzer and pushes it into a cartridge where medium to high molecular weight hydrophobic toxins are adsorbed. The purified ultrafiltrate is then returned to the blood flow before it enters the second diffusive chamber.

Specificities of Disposables Required

Blood tubing set is characterized by the cassette system, which limits tubing connections, reduces extracorporeal blood volume, and allows automatic loading and unloading of pump segments and blood lines.

Phylther HF series dialyzers (for which auto-Qinf is optimized) or other high flux dialyzers can be used. *Olpur MD190*/*MD220* are available, in which substitution fluid is infused through a fifth port into the dialyzer. HFR/SUPRA dialyzers consist of a double chamber filter characterized by either a high flux (*HFR*) or super-high permeability membrane (*SUPRA*) in the first chamber, followed by a second diffusive chamber. A cartridge filled with hydrophobic resin and special blood lines complete the extracorporeal circuit.

Dialyclean and *H_2OClean* are *Polyphenylene*® hollow-fibre ultrafilters sterilized by ethylene oxide for dialysis fluid and infusion fluid, tested for a 400 working-hour life on a daily usage. In *Dialyclean*, a transponder identifies the filter with a unique code, which records the filter as *used*. This guarantees it cannot be used beyond the foreseen life-time, or reused.

Additional Therapeutic Options

Flexya offers several therapeutic options, such as:

- *Natrium* sensor: derives plasma sodium concentration from plasma water conductivity measures in HFR/SUPRA treatments;
- *Aequilibrium* application: helps to reduce the incidence of hypotensive phenomena and disequilibrium syndrome, controlling plasma sodium via weight loss rate and conductivity profiles. *Aequilibrium* can be used with HFR, standard hemodialysis and HDF treatments;
- Thermal balance: helps keep a stable patient temperature, by means of the *Hemox* temperature measurements on the arterial bloodline to establish the temperature of the dialysis solution.

Additional Monitoring Options

Treatment trends and patient condition, exploiting sensors installed on Flexya monitor, are monitored and controlled in several ways:

- *Kt*/*V* application measures some of the efficacy parameters of the treatment (Clearance, Kt, Kt/V), using conductivity measures and steps method;
- Blood pressure and heart rate are monitored via a sphygmomanometer;
- *Hemox* optical sensor, applied on a special cuvette in the blood lines, continuously measures hematocrit, oxygen saturation, and blood temperature;

- Blood volume variations from baseline, derived from hematocrit measures;
- *SOGLIA* [6] warns for potential onset of hypotensive drops in the patient, using oxygen saturation standard deviation monitoring;

Cleaning and Disinfection

In order to eliminate contamination and avoid biofilm formation within the hydraulic circuit, the following protocol is recommended: chemical disinfection with Oxagal (peracetic acid and oxygen peroxide based) after each treatment, alternating heat or chemical disinfection at the end of the day, a descaling procedure (citric acid at high temperature) at least once per week, and chemical disinfection with dwelling of the chemical agent during the weekend.

Risk Management System

Although one ultrafiltration stage is enough for depuration purposes, a second stage is required by risk analysis to provide redundant safety and a "first-failure proof" philosophy. The integrity of both ultrafilters is tested before each treatment, while continuous pressure monitoring is performed during dialysis and cleaning sessions.

Flexya measures standard fistula and venous restitution pressure, pre-dialyzer pressure, pre- and post-infusion pump pressure. Together with the peristaltic pump speed control and blood sensor monitoring, this allows complete control over the extracorporeal circuit behavior. Likewise, flow measurements, eight pressure measurements, tests on ultrafilters and *differential flow meter*, redundancy and tests on conductivity and temperature probes allow proper functioning and control of the hydraulic circuit.

Display of Settings and Connection to Hospital Information System

All results produced by such applications can be observed on different graphs plotted on the Flexya screen (Figs. 7.2 and 7.3). Alarm thresholds can be used for blood pressure, heart rate, hematocrit, oxygen saturation, and volume variation. Data are available for shared authorized access through the hospital information systems on Ethernet port, and in specific cases for download on the patient's card via RFiD data transmission.

Cost Assessment

As a differential cost observation, on line priming, boluses and restitution give operators the possibility to completely avoid solution bags.

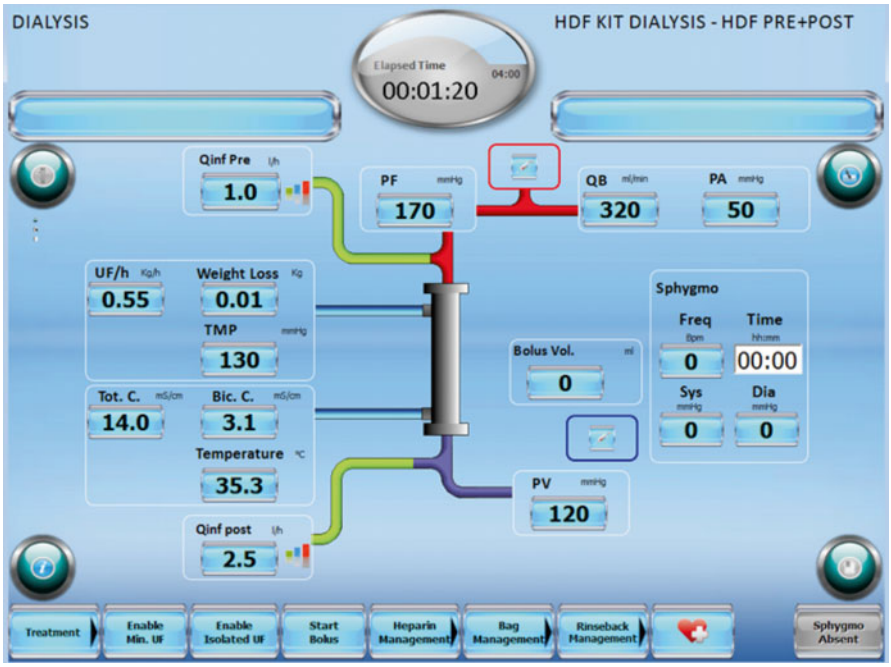


Fig. 7.2 Main page snapshot

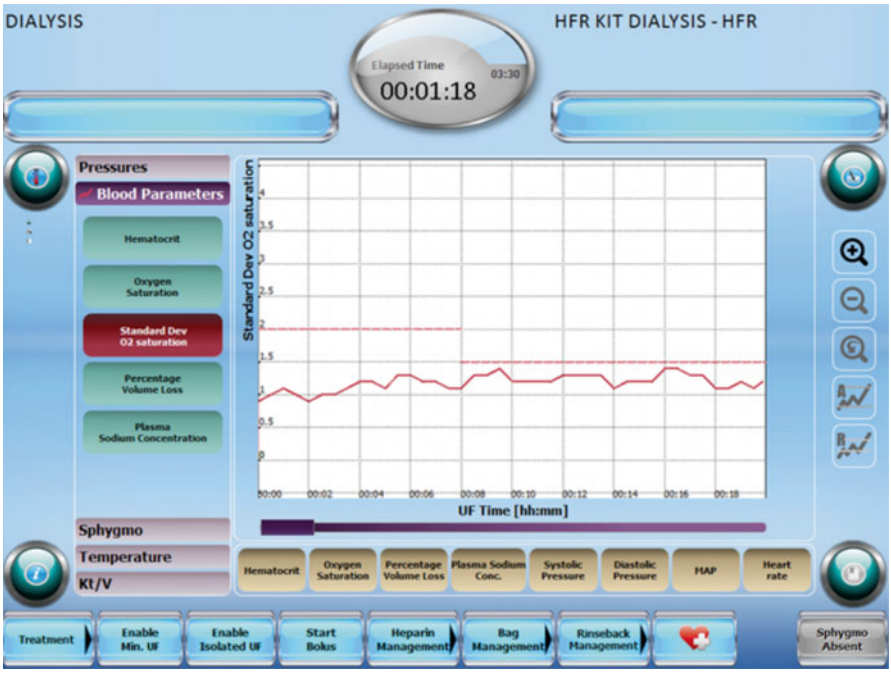


Fig. 7.3 Blood parameters graph page snapshot

References

1. Maduell F, et al. Mid-dilution hemodiafiltration: a comparison with pre- and postdilution modes using the same polyphenylene membrane. Blood Purif. 2009;28:268–74.
2. Eloot S, et al. Removal of water-soluble and protein-bound solutes with reversed mid-dilution versus post-dilution haemodiafiltration. Nephrol Dial Transplant. 2012;27:3278–83.
3. Borrelli S, et al. Effect of hemodiafiltration with endogenous reinfusion on overt idiopathic chronic inflammation in maintenance hemodialysis patients: a multicenter longitudinal study. Hemodial Int. 2014;18:758–66.
4. Memoli B, et al. Evidence that p-cresol and IL-6 are absorbed by the HFR cartridge: towards a new strategy to decrease systemic inflammation in dialyzed patients? PLoS One. 2014;9:e95811.
5. Pasquali S, et al. A novel option for reducing free light chanins in myeloma kidney: supra-hemodiafiltration with endogenous reinfusion (HFR). J Nephrol. 2015;28:251–4.
6. Mancini E, et al. The oxygen saturation Italian Study Group: final results. Proceedings of the 49th ERA-EDTA congress, 2012, France. Nephrol Dial Transplant. 2012;27 Suppl 2:ii48–9.

Chapter 8
Online Hemodiafiltration by Fresenius Medical Care

Bernard Canaud, Pascal Kopperschmidt, Reiner Spickermann, and Emanuele Gatti

Abstract Hemodiafiltration has been identified by Fresenius Medical Care (FMC) as a vital need to improve care and outcome of chronic kidney disease patients. By enhancing the removal of middle molecular uremic toxins and improving hemodynamic and global tolerance of dialysis sessions, HDF was recognized as an efficient dialysis modality and a mean to improve patient treatment perception and reduce disease burden. By providing fluid substitution online, HDF appeared the only economically and technically long-term viable solution. Online HDF therapy has been a major R&D focus for FMC over the last decades leading to the development of several online HDF machines with different features.

Keywords AutoSub Plus • Disinfection • High volume HDF • Online hemodiafiltration • Predilution • Postdilution • Substitution fluid • Transmembrane pressure

Introduction

Hemodiafiltration has been identified by Fresenius Medical Care (FMC) as a vital need to improve care and outcome of chronic kidney disease patients [1]. By enhancing the removal of middle molecular uremic toxins and improving hemodynamic

B. Canaud, PhD (✉)
Emeritus Professor of Nephrology, Center of Excellence Medical, Fresenius Medical Care Deutschland GmbH, Else-Kröner-Straße 1, Bad Homburg v.d.H. 61352, Germany

University of Montpellier, School of Medicine, Montpellier, France
e-mail: Bernard.Canaud@fmc-ag.com

P. Kopperschmidt, PhD • R. Spickermann
Department of Global Research and Development,
Fresenius Medical Care Deutschland GmbH, Bad Homburg v.d.H., Germany

E. Gatti
Department of Health Sciences and Biomedicine, Danube University Krems,
Krems, Austria

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_8

and global tolerance of dialysis sessions, HDF was recognized as an efficient dialysis modality and a mean to improve patient treatment perception and reduce disease burden. By providing fluid substitution online, HDF appeared the only economically and technically long-term viable solution [2]. Online HDF therapy has been a major R&D focus for FMC over the last decades leading to the development of several online HDF machines with different features [3], see Fig. 8.1.

Water Treatment System Required

The water treatment system for hemodialysis and hemodiafiltration shall be designed on knowledge of the feed water characteristics. This system should ensure a water quality at the dialysis machine inlet complying to applicable national standards, as well as the international ISO 13959 standard (Water for haemodialysis and related therapies). Concentrates must meet the requirements of ISO 13958 (Concentrates for haemodialysis and related therapies), and the produced dialysis fluid those of the ISO 11663 standard (Quality of dialysis fluid for haemodialysis and related therapies).

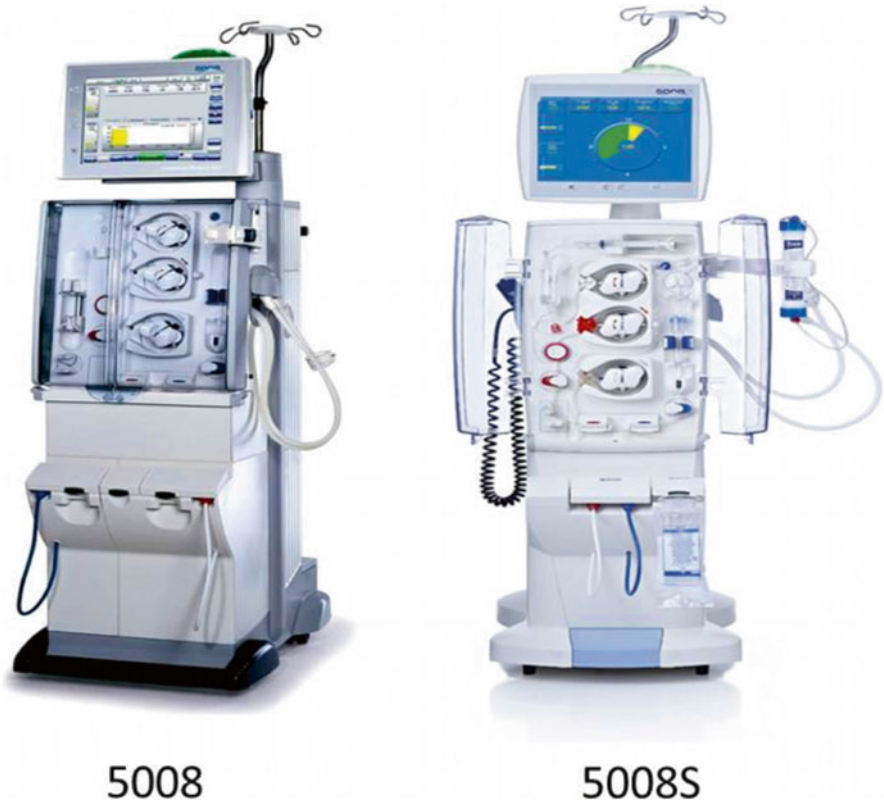


Fig. 8.1 HDF machine

Short Description and Outline of the HDF Machine

Touch screen is ensuring a user-friendly interface and displaying useful information (technical, therapeutical) user specific; a hydraulic circuit designed to produce electrolytic dialysis and substitution fluids in compliance with technical requirements and medical prescription; blood and hydraulic (dialysate and infusion) circuits activated by adjustable pumps and secured by appropriate sensors. In addition, the dialysate circuit includes a volumetric balance chamber.

State of the art HDF technology benefits from a hydraulic branch delivering online prepared substitution fluid. Drawn from fresh dialysis fluid by utilization of a specially designed ultrafilter, substitution fluid is filter-sterilized and depyrogenated. Since the substitution is a fraction of the dialysate fluid pathway, the patients' fluid balance is assured in hydraulics using a volumetric balance chamber, which was a standard in Fresenius dialysis machines from the beginning. All fluid pathways are tested against fluid leakages before and disinfected after the treatment. Technical features of the 5008 dialysis machine are summarized in Table 8.1.

HDF Prescription Modality (Manual/Automatic)

Considering that blood flow, treatment time and weight loss are set according to medical treatment, HDF prescription may be performed in manual or automatic mode [4]. In *manual mode*, the user deselects the "AutoSub plus" function (5008 machines) and sets the substitution pump to the desired flow. In *automatic mode*, the user selects the substitution mode (post, pre or mixed) depending on the HDF machine type, and the monitor will run automatically the session targeting to adjust substitution volume while keeping transmembrane pressure in a safe range. The substitution flow rate is adjusted automatically in consideration of blood viscosity, membrane size and fiber geometry, see snapshot of screen in Fig. 8.2. The Fresenius 5008 dialysis machine, equipped with 'AutoSub plus' allows to maximize HDF substitution volumes without treatment discontinuation by hemoconcentration-related alarms [5]. A dialyzer stress test by permanent analysis of static and dynamic pressures using extracorporeal and hydraulic sensors optimizes infusion rate for each patient individually.

Consequently, high volume HDF is feasible in routine clinical practice [6]. By running HDF machine in 'AutoSub plus' mode, filtration fraction can be increased up to 30–35 % and total substitution volume by 13–20 % in post dilution mode [7].

HDF Modalities

Post and predilution modalities can be run indifferently on the same HDF machine equipped with two pumps (for blood flow, and for substitution flow). Mixed-dilution modality requires a specific three pumps HDF machine (for blood flow, postdilution

Table 8.1 Technical features of the 5008 online HDF machine

Technical features	5008 online HDF (Fresenius)
Blood pump flow range (ml/min)	30–600 ml/min
Dialysate flow (ml/min)	0; 100–1000 ml/min
Dialysate flow selection mode	Manual; eco-flow; auto flow
Emergency button	Yes
Substitution mode: manual/automatic	Manual or automatic (AutoSub plus)
Settable parameter(s) in volume control mode	Substitution rate (ml/min); target substitution volume (L)
Substitution fluid flow range	0–200 ml/min (0–1.2 L/h)
Electrolyte concentration adjustment	Pre-selected concentrates of Na and HCO3 in mmol/L
Substitution fluid delivery options	Predilution, postdilution, mixed dilution
Online priming, rinsing, IV bolus	Yes
Stationary ultrafilters	Yes, 2, Diasafe and online filter
Additional ultrafilter	No
Integrity pressure test ultrafilter	Yes
Blood access monitoring	Yes
Online clearance monitoring	Yes (OCM)
Blood volume monitoring (BVM)	Yes, optional
Blood temperature monitoring	Yes, optional
Other monitoring options	Yes, BVM, BTM, OCM
Alarm and information signals	Yes, blood circuit leakage, pressure alarms, dialysate composition, pressure test failure
IT connectivity	Yes,
Data transfer via patient card	TDMS
Standard safety features	Yes, complying to international standards
Advanced safety features	Yes, early detection of bleeding by dynamic pressure monitoring (DPM), leakage sensors on hydraulic circuit; optional: vascular access monitoring dislodgement (VAM)
Touchscreen operation and ergonomic design	Yes
Special features	Feedback controlled BVM/BTM

and predilution). Management of flow pumps is ensured by pressure sensors (prefilter, venous, hydraulic), integrated microprocessors and proprietary software that track continuously substitution flow and TMP and react in adjusting pre and postdilution flows to keep TMP in safe range [8].

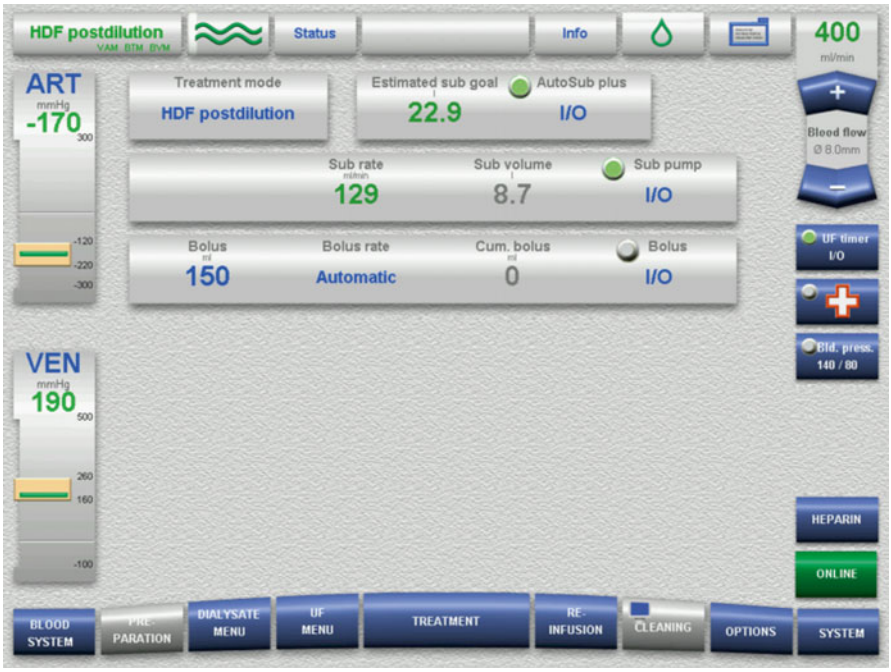


Fig. 8.2 Snapshot of screen I

Specificities of Disposables Required

Hemodiafilters are typically not captive of the blood tubing set. All high-flux hemodialyzers, validated for online-HDF, can be used on FMC machines. It is mandatory to assess clinically the currently used hemodiafilter to ensure that performance (ultrafiltration and solutes clearance) and albumin loss are in the targeted range and conform to manufacturer description. Fresenius FX/F hemodiafilters have been tested and validated for this application [5, 9–11].

Specifically designed and featured with membrane characteristics that ensure sterile filtration of dialysis and substitution fluids, are proprietary and captive of HDF machines. Two such ultrafilters are inherent to the HDF machine, the first (Diasafe) is placed on the inlet dialysis fluid circuit and the second (Online Filter) is placed on the substitution circuit. The Diasafe filter is flushed regularly during the treatment. The Online filter operates in cross-flow mode. The membranes' integrity, qualified for 100 consecutive treatments, is assessed by a pressure holding test prior to dialysis [4].

Additional Therapeutic Options

Several additional technical features are basic or optional part of Fresenius HDF machines.

- Blood temperature monitoring (BTM) (option) may be used for controlling thermal balance of dialysis patient (isothermic, cooling) and reducing hemodynamic instability (reducing intradialytic hypotensive episodes), and can be used to measure blood access recirculation [4].
- Blood volume monitoring (BVM) (option) is used to assess blood volume reduction induced by ultrafiltration. BVM relies on an ultrasound sensor coupled to the arterial blood tubing set that measures hematocrit associated blood density changes. This measurement of relative blood volume changes during HDF provides a tool to estimate blood volume refilling capacity and a patient threshold limit for ultrafiltration [12].

Additional Monitoring Options

- To determine ionic dialysance after modulation of electrolyte concentration, online clearance measurement (OCM) is intermittently applied and the clearance or dose is displayed throughout the session, see Fig. 8.3. OCM provides

Fig. 8.3 Snapshot of screen 2

quite reliable values reflecting urea clearance, and is used as surrogate of dialysis dose delivered. It has been validated in online HDF with large substitution volumes [12].
- Feedback controlled BVM may facilitate treatment of hypotensive prone patients. The relative blood volume change is tracked during the session, and based on threshold limit set by the user, the algorithm of the HDF machine reacts in adjustment of ultrafiltration according to the refilling capacity of the patient [13].

Cleaning and Disinfection

Several disinfection procedures have been validated and released for Fresenius HDF dialysis machines, e.g. Citrosteril™ heat disinfection or Puristeril™ cold disinfection.

Risk Management System

Safety Features

HDF machines are equipped with all safety devices required by standards to ensure maximum safety to patients and staff. The online substitution supply system in FMC Online HDF dialysis machines benefits from a redundant safety setup. In the unlikely case of a leaking ultrafilter during treatment the concomitant filter still ensures sterility.

Display of Settings and Connection to Hospital Information System

The Fresenius Therapy and Data Management System (TDMS) consist of a set of applications linked to the dialysis machine network providing pre-setting of therapeutic parameter and treatment documentation. Data management associated with the HDF therapy is supported by TDMS.

Cost Assessment

Cost of HDF treatment relies on three main components: (1) Online HDF machine and technical feature options; (2) Disposable tubing sets and sterilizing ultrafilters; (3) Microbiological monitoring of water and dialysis fluid [14]. Points 1 and 2 will not be disclosed here since they are country specific and market related. Point 3 is

certainly the more sensitive one. In Fresenius HDF machine, blood tubing and substitution tubing lines are presented as single use disposable and proprietary sets. No additional and final sterilizing filter is required on the substitution line. The two sterilizing ultrafilters have to be replaced after 100 treatments or every 3 months. This cost benefit has been recently confirmed in an independent study showing that extra cost per treatment session was the lowest (−1.29 €) among assessed HDF therapies [15].

References

1. Canaud B, N'Guyen QV, Lagarde C, et al. Clinical evaluation of a multipurpose dialysis system adequate for hemodialysis or for postdilution hemofiltration/hemodiafiltration with online preparation of substitution fluid from dialysate. Contrib Nephrol. 1985;46:184–6.
2. Roy T. Technical and microbiological safety of online hemodiafiltration: a European perspective. Semin Dial. 1999;12:81–7.
3. Operating Instructions Fresenius MT 2008 ON-LINE-HDF 2/05.91 (OP), Operating Instructions Fresenius MT 4008 ON-LINE-HDF(4008) 1/12.93 (GA), Operating Instructions Fresenius Medical Care 4008 Onlineplus 5/12.98 (OP), Operating Instructions Fresenius Medical Care 5008 (OP) 3/08.05.
4. Operating Instructions Fresenius Medical Care 5008 (OP-EN) 10/08.13.
5. Potier J, Le Roy F, Faucon JP, et al. Elevated removal of middle molecules without significant albumin loss with mixed-dilution hemodiafiltration for patients unable to provide sufficient blood flow rates. Blood Purif. 2013;36:78–83.
6. Marcelli D, Scholz C, Ponce P, et al. High-volume postdilution hemodiafiltration is a feasible option in routine clinical practice. Artif Organs. 2015;39:142–9.
7. Maduell F, Rodríguez N, Sahdalá L, et al. Impact of the 5008 monitor software update on total convective volume. Nefrologia. 2014;34:599–604.
8. Pedrini LA, De Cristofaro V, Pagliari B, Samà F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000;58:2155–65.
9. Ahrenholz PG, Winkler RE, Michelsen A, et al. Dialysis membrane-dependent removal of middle molecules during hemodiafiltration: the beta2-microglobulin/albumin relationship. Clin Nephrol. 2004;6:21–8.
10. Maduell F, Arias-Guillen M, Fontsere N, et al. Elimination of large uremic toxins by a dialyzer specifically designed for high-volume convective therapies. Blood Purif. 2014;37:125–30.
11. The new 5008 Cordiax F00005533 GB (BG 08.13) © Copyright 2013 Fresenius Medical Care Deutschland GmbH.
12. Gross M, Maierhofer A, Tetta C, et al. Online clearance measurement in high-efficiency hemodiafiltration. Kidney Int. 2007;72:1550–3.
13. Schneditz D, Levin NW. Non-invasive blood volume monitoring during hemodialysis: technical and physiological aspects. Semin Dial. 1997;10:166–9.
14. Oates T, Cross J, Davenport A. Cost comparison of online haemodiafiltration with high-flux haemodialysis. J Nephrol. 2012;25:192–7.
15. Lebourg L, Amato S, Toledano D, et al. Online hemodiafiltration: is it really more expensive? Nephrol Ther. 2013;9:209–14.

Chapter 9
Nikkiso Hemodiafiltration Equipment

Daisuke Toshigami, Uwe Rogalla, and Yoshiro Ueda

Abstract Observing the development of HDF patient numbers on a global scale between 2004 and 2010, the number of HDF patients increased by around 13 % per year. Online HDF was by far the predominant mode of HDF therapy, being applied to around 90 % of HDF patients in 2010. In this situation, NIKKISO has developed the "DBB-07" Dialysis System, which is focused on online-therapies. In this chapter the DBB-07 features will be explained.

Keywords Blood Volume Monitor (BVM) • Dialysis Dose Monitor (DDM) • Disinfection • Online hemodiafiltration • Predilution • Postdilution • Substitution fluid • Transmembrane pressure

Introduction

Observing the development of HDF patient numbers on a global scale between 2004 and 2010, the number of HDF patients increased by around 13 % per year [1]. Online HDF was by far the predominant mode of HDF therapy, being applied to around 90 % of HDF patients in 2010. In this situation, NIKKISO has developed the "DBB-07" Dialysis System, which is focused on online-therapies, see Fig. 9.1. In this chapter the DBB-07 features (see Fig. 9.1.) will be explained.

D. Toshigami (✉)
Technical Department, NIKKISO Europe GmbH, Langenhagen, Lower Saxony, 30855, Germany
e-mail: d.toshigami@nikkiso-europe.eu

U. Rogalla
Department of Sales and Marketing, NIKKISO Europe GmbH, Langenhagen, Lower Saxony, Germany

Y. Ueda
NIKKISO Europe GmbH, Langenhagen, Lower Saxony, Germany

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_9

Fig. 9.1 Dialysis machine

Water Treatment System Required

The water treatment system for hemodialysis and hemodiafiltration shall be designed on the knowledge of the feed water characteristics. This system should ensure a water quality at the dialysis machine inlet complying to applicable national standards, as well as the international ISO 13959 standard (Water for haemodialysis and related therapies). Concentrates must meet the requirements of ISO 13958 (Concentrates for haemodialysis and related therapies), and the produced dialysis fluid those of the ISO 11663 standard (Quality of dialysis fluid for haemodialysis and related therapies).

Short Description and Outline of the HDF Machine

Hydraulic prescription: In the DBB-05, a specific tubing line with single use dialysis fluid filter (EFL-015) is needed for online HDF, and the prepared dialysis fluid passes only one EF-02D filter before supplying fluids to the dialyser. The hydraulic system of the DBB-07 has been upgraded with an additional dialysis fluid filter (EF-02D) to ensure a quality of dialysis and substitution fluid complying with international standards [2].

Dialysis fluid and substitution fluid: In contrast to conventional HDF treatments (with bags), the substitution fluid used for the online HDF treatment is taken from the dialysis machine. The adjusted conductivity and temperature are continuously checked by independent monitoring systems to ensure safe operation. After passing two EF-02D filters, ultrapure substitution fluid is then supplied to the blood circuit using the substitution pump. The DBB-07 has a function called 'Flow application' whereby the flow rate of the dialysis fluid through the dialyser will not be influenced by the branched substitution fluid.

Technical aspects of fluid balance: The ultrafiltration rate in the dialyser is determined by the substitution fluid flow rate and the intradialytic weight loss of the patient.

To control the dialysis fluid flow and the removed ultrafiltration volume, the DBB-07 has a closed loop system consisting principally of a duplex pump, an ultrafiltration pump and solenoid valves. The duplex pump is a volumetric instead of a chamber system, supplying and draining the same amount of dialysate to and from the dialyser. Technical features of the DBB-07 dialysis machine are summarized in Table 9.1.

HDF Prescription Modality (Manual/Automatic)

The maximum substitution fluid rate is limited depending on the selection of pre- or post-dilution and blood flow rate, in order to limit the hemoconcentration in the blood compartment. It is possible to link the blood flow rate with substitution fluid rate by ratio setting. Dependent on whether pre- or post-dilution is performed, the substitution rate is governed by the blood pump speed.

HDF Modalities

The external scale offers at the moment the most flexible system for dialysis therapies. The DBB-07 with external scale can perform online treatments, see Fig. 9.2, but also HDF (predilution or postdilution), HF and Acetate-Free Biofiltration (AFB) treatments with solution bags. AFB is a special kind of treatment without acetate and bicarbonate in the dialysate.

Table 9.1 Technical features of the DBB-07 dialysis machine

Technical features	DBB-07 (Nikkiso)
Blood pump flow range (ml/min)	40–600 ml/min
Dialysate flow (ml/min)	300–700 ml/min
Dialysate flow selection mode	Steps 1 mL/min
Emergency button	Bolus key and minimum UF key
Substitution mode: manual/automatic	Automatic (ratio of blood flow)
Settable parameter(s) in volume control mode	Substitution ratio (%), substitution rate (ml/min), target substitution volume (L)
Substitution fluid flow range	0.00; 0.10–18.00 L/h (OHDF)
	0.00; 0.10–30.00 L/h (OHF)
Electrolyte concentration adjustment	Yes
Substitution fluid delivery options	Pre, post
Online priming, rinsing, IV bolus	Yes
Stationary ultrafilters	Yes, 2 EF-02D filters
Additional ultrafilter	No
Integrity pressure test ultrafilter	Filter test for leakage and clogging of filters
Blood access monitoring	Pressure and Kt/V measurement
Online clearance monitoring	Yes, optional
Blood volume monitoring (BVM)	Yes (Haemo-Master), optional
Blood temperature monitoring	No
Other monitoring options	Blood pressure monitor, optional
Alarm and information signals	4 lights external status display; alarm and information display with help message; outlet for alarm output
IT connectivity	Yes, optional
Data transfer via patient card	No
Standard safety features	Complying to international standards
Advanced safety features	Dialyser inlet pressure measurement, as an indication of hemoconcentration in the dialyser; Clean Coupling® for better hygiene; continuous monitoring system of a closed loop system (valves check function for safety); disinfectable concentrate suction nozzles
Touchscreen operation and ergonomic design	Yes
Special features	Flow application: the dialysis fluid flow is not influenced by the branched substitution fluid; external scale for H(D)F or AFB with bags, eco-friendly concentrate-, water- and energy- saving mode; optimized energy use as standard via integrated heat-exchangers; customizable operating screen

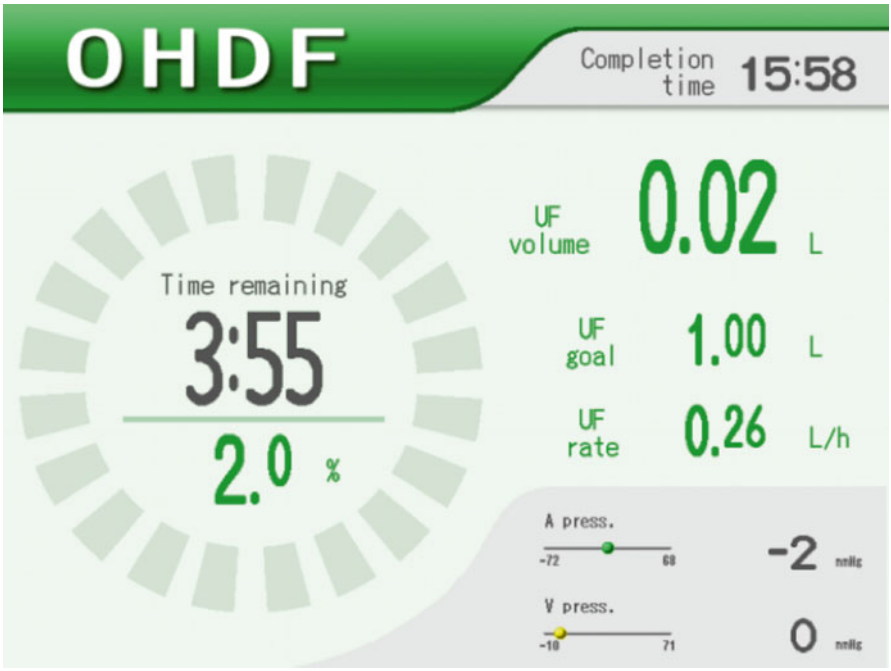


Fig. 9.2 Snapshot screen I

Specificities of Disposables Required

- Hemodiafilters

  The DBB-07 is compatible with commercially available dialysers that are equipped with standard dialysis fluid and blood connection (ISO8637).

- Blood tubing sets

  The steam sterilized blood tubing lines (AV-06 series) and Online HDF line (C07J-P) can be used on DBB-07 with OHDF. The shunt lock connector cap (for A/V line) is equipped with an integrated discharge hook. The capless hydrophobic filters and the perfectly fitting blood tubing lines facilitate the set-up of the DBB-07.

- Ultrafilters

  The membrane used for the EF-02D is Polyester Polymer Alloy (PEPA®), which is a unique membrane with a specially developed three-layer structure, providing excellent protection against endotoxins and their fragments. Using a fluorescent endotoxin marker in laboratory tests, it has been shown that endotoxins are safely retained [3, 4].

Additional Therapeutic Options

- Blood Volume Monitor (BVM, Haemo-Master)

  The BVM continuously measures the relative blood-volume during the treatment. This is the basis for the automatic regulation system Haemo-Master, which controls the conductivity and ultrafiltration rate (UF rate). The intelligent interplay of the regulation of the conductivity and UF rate adapts the blood volume changes to the ideal curve for the specific patient, in order to prevent hypotensive episodes during the treatment. This option can be combined with all treatments; see Fig. 9.3 for a snapshot of the screen.

Additional Monitoring Options

- Blood Pressure Measurement (BPM)

  Continuous blood pressure measurement can be carried out during treatment, and monitored as a course chronologically on the screen. An automatic deactivation of the UF rate also occurs when the pre-selected pressure limits are reached.

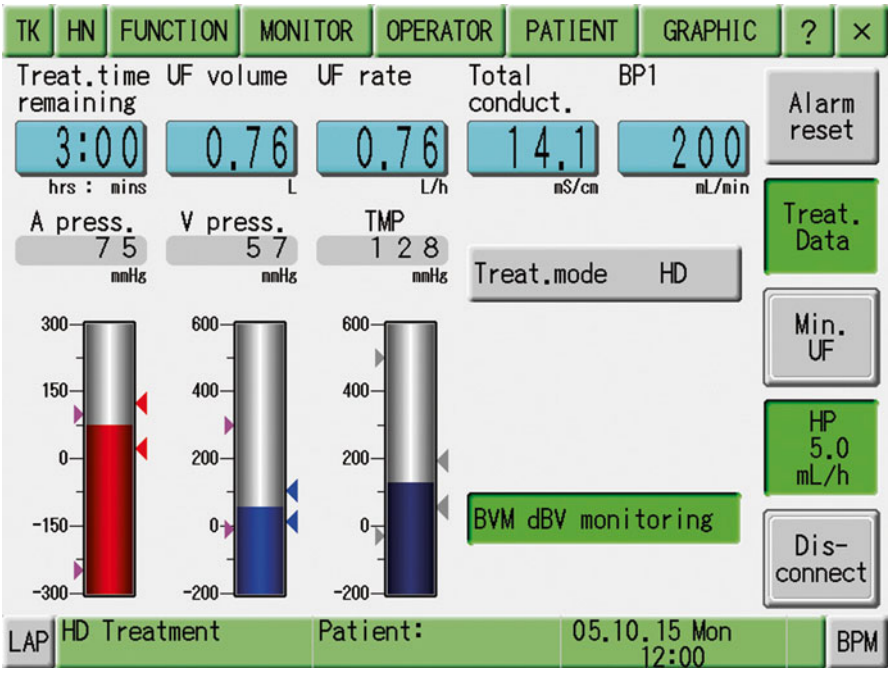


Fig. 9.3 Snapshot screen II

- Dialysis Dose Monitor (DDM)

  DDM can monitor Kt/V continuously without interruption of the treatment and is easy to handle. It is activated automatically after entering the parameters. It is not necessary to enter the distribution volume, which is normally estimated using approximation formula to display expected accurate results.

Cleaning and Disinfection

The DBB-07 must have a disinfection with citric acid (50 %), or a chemical disinfection with peracetic acid or sodium hypochlorite before each on-line HDF/HF treatment. To optimize the hygiene of the dialysis fluid circuit NIKKISO has integrated the concentrate suction nozzles and patented Clean Couplings® into the disinfection cycle.

Risk Management System

- Continuous monitoring system of a closed loop system (see Short description and outline of the machine)

  To ensure the accuracy of the closed system and ensuring no leakage during the treatment, the DBB-07 monitors hydraulic pressure as well as conductivity across the solenoids, duplex pump and ultrafiltration pump valves.

- Dialyser inlet blood pressure (DIP)

  The extracorporeal circuit of the DBB-07 incorporates dialyser inlet blood pressure measurement. This enables an accurate TMP measurement and an indication of hemoconcentration in the dialyser, which is especially useful whilst carrying out high volume online HDF.

Display of Settings and Connection to the Hospital Information System

Data and information from the treatment procedure are sent simply and conveniently to the hospital information system via the hospital network. The DBB-07 offers various interfaces for main software solutions with an experienced partner in the market.

Cost Assessment

Please see below comparison table.

Consumables	DBB-05		DBB-07	
	HD	Online HDF	HD	Online HDF
Blood tubing lines and dialyser	X	X	X	X
Single dialysis fluid filter (EF-02D)	X	X	–	–
Double dialysis fluid filters (two EF-02Ds)	–	–	X	X
Substitution line with single use filter (EFL-015)	–	X	–	–
Substitution line without single use filter (C07J-P)	–	–	X	X
Saline bag	X	–	–	–
Cost assessment	100 %	300 %	100 %	100 %

Conclusion

The DBB-07 provides HD, HF, HDF, OHF and OHDF with a safe system, reducing any risk to the patient, along with helpful monitoring functions of the patients condition. This enables the operator to closely customize the treatment to the patients needs. When HDF is selected for a patient, an operator has to prepare the disposables and the device for HDF. The operators workload could increase in the future as the number of HDF patients is increasing. To make HDF therapies economical, easy to set up and assessable to all, NIKKISO are continuously developing their systems to meet todays needs.

References

1. Sichart JM, Moeller S. Utilization of hemodiafiltration as treatment modality in renal replacement therapy for end-stage renal disease patients – a global perspective. Contrib Nephrol. 2011;175:163–9.
2. ISO 11663. Quality of dialysis fluid standard for haemodialysis and related therapy; 2009.
3. Hayama M, et al. Optimum dialysis membrane for endotoxin blocking. J Membr Sci. 2003;219:15–25.
4. Hayama M, et al. Visualization of distribution of endotoxin trapped in an endotoxin-blocking filtration membrane. J Membr Sci. 2002;210:45–53.

Chapter 10
Nipro Online Hemodiafiltration System: Surdial™-X

Matteo Lavezzini

Abstract The Surdial-X, manufactured by Nipro, is a dialysis machine that can be equipped with one, two, or three pumps. In its HDF configuration, the machine permits double needle online HDF, in pre and post dilution, as well as single needle online HDF in pre and post dilution. All therapies can be carried out with different ultrafiltration, bicarbonate and sodium profiles. A 15 inch touch screen display allows straightforward operations, properly assisting users with full-text guidance. The Surdial-X comes standard with two innovative techniques: Clean Treatment Start (CTS) and Dialysate Infusion Function (DIF). This last one permits the use of the typical online functions even without using the HDF circuit, extending their benefits also to regular HD treatments.

Keywords Clean treatment start (CTS) • Dialysate infusion function (DIF) • Disinfection • Online hemodiafiltration • Predilution • Postdilution • Substitution fluid • Transmembrane pressure

Introduction

The Surdial-X, manufactured by Nipro, is a dialysis machine that can be equipped with one, two, or three pumps. In its HDF configuration, the machine permits double needle online HDF, in pre and post dilution, as well as single needle online HDF in pre and post dilution. All therapies can be carried out with different ultrafiltration, bicarbonate and sodium profiles. A 15 inch touch screen display allows straightforward operations, properly assisting users with full-text guidance. The Surdial-X comes standard with two innovative techniques: Clean Treatment Start (CTS) and

M. Lavezzini, M.Sc. Eng.
Department of Marketing, Nipro Europe N.V., Weihoek 3H, Zaventem 1930, Belgium
e-mail: Matteo.Lavezzini@nipro-europe.com

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_10

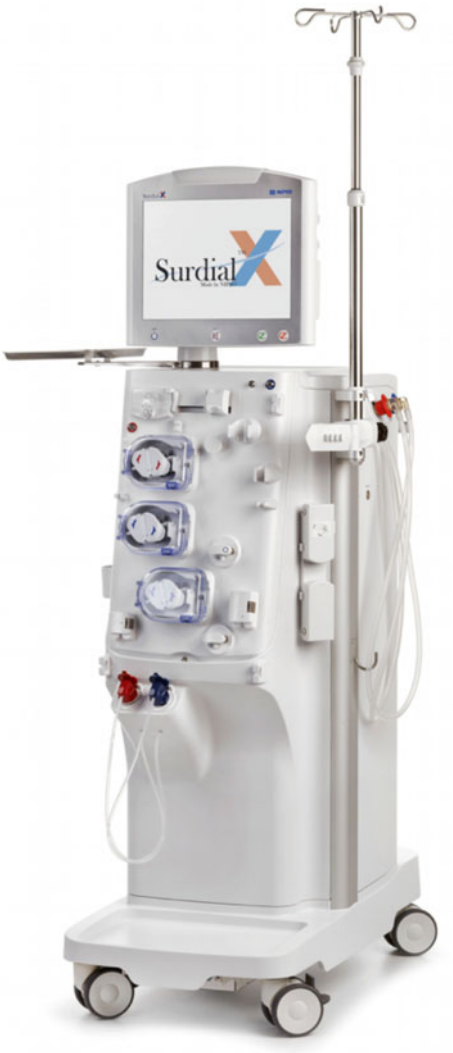


Fig. 10.1 Dialysis machine

Dialysate Infusion Function (DIF) (see Fig. 10.1). This last one permits the use of the typical online functions even without using the HDF circuit, extending their benefits also to regular HD treatments.

Water Treatment System Required

The water treatment system for hemodialysis and hemodiafiltration shall be designed on knowledge of the feed water characteristics. This system should ensure a water quality at the dialysis machine inlet complying to applicable national standards, as well as the international ISO 13959 standard (Water for haemodialysis and related

therapies). Concentrates must meet the requirements of ISO 13958 (Concentrates for haemodialysis and related therapies), and the produced dialysis fluid those of the ISO 11663 standard (Quality of dialysis fluid for haemodialysis and related therapies).

Short Description and Outline of the HDF Machine

The Surdial-X is a machine used for the treatment of patients with acute or chronic renal failure. In its HDF configuration, the machine has a dedicated substitution pump, assuring the correct fluid flow through a specific bloodline for HDF. To grant the appropriate purity of the dialysate fluid, the machine relies on two endotoxin retention filters (cut filters). The dialysis fluid will pass through the first filter just after its preparation and subsequently through a second filter just prior to infusion into the bloodline, as substituting fluid. The appropriate fluid balance is obtained with the action of two internal chambers. Technical features of the Surdial-X dialysis machine are summarized in Table 10.1.

HDF Prescription Modality

In the HDF settings, the Surdial-X permits double needle online HDF, in pre and post dilution, as well as single needle online HDF in pre and post dilution. In case of the single needle format, the machine must be configured with a third pump, specific for this treatment. All therapies can be carried out with different ultrafiltration, bicarbonate and sodium profiles. The substitution volume can be managed automatically or manually. In this last case, the operator just has to program the desired substitution volume and time.

HDF Modalities

Independent of the type of HDF treatment (pre or post dilution), a specific online screen in the interface permits to manage the online function menu, setting the target fluid replacement volume and rate, as well as the parameters for bolus injection, see Fig. 10.2. The auto-sub function prevents hemo-concentration and clotting: the machine changes the substitution fluid pump flow according to the blood pump flow, permitting automated fluid replacement.

Specificities of Disposables Required

The Surdial-X needs to be equipped with disposables for an accurate dialysis treatment, including blood tubing sets, ultrafilters and hemodialyzers.

Table 10.1 Technical features of the Surdial™-X dialysis machine

Technical features	Surdial™-X (Nipro)
Blood pump flow range (ml/min)	10–600 ml/min
Dialysate flow (ml/min)	100–800 ml/min
Dialysate flow selection mode	Yes (including link with blood flow)
Emergency button	Yes
Substitution mode: manual/automatic	Manual/automatic
Settable parameter(s) in volume control mode	0.00–720.0 L as substitution volume
Substitution fluid flow range	0, 10–500 mL/min
Electrolyte concentration adjustment	Yes, concentration of Na + Electrolyte for conductivity control (0.0, 3.0–20.0 mS/cm)
Substitution fluid delivery options	Postdilution, predilution
Online priming, rinsing, IV bolus	Yes
Stationary ultrafilters	Yes, 2 for HDF (CF-609 N)
Additional ultrafilter	Not needed
Integrity pressure test ultrafilter	Yes
Blood access monitoring	Yes (control to arterial and venous pressure)
Online clearance monitoring	Calculation through Kt/V dose finder
Blood volume monitoring (BVM)	Under development
Blood temperature monitoring	Not available
Other monitoring options	Blood pressure monitoring
Alarm and information signals	Yes, available as visual alarm (3 colors light indicator), audible alarm (five stage setting of sound intensity) and text messages on the touch screen interface
IT connectivity	Yes, export of data to external software with .XML or .HL7 files
Data transfer via patient card	Yes
Standard safety features	Venous pressure monitor, arterial pressure monitor, venous clamp, arterial clamp, blood leak detector, bubble detector, temperature monitor, conductivity monitor, blood pump monitor, UF monitor, TMP monitor, dialysate pressure monitor, close circuit test
Advanced safety features	Leakage sensor for hydraulic parts, leakage sensor for extracorporeal circuit, substitution port connection test
Touchscreen operation and ergonomic design	Yes
Special features	Clean treatment start, dialysate infusion function, single needle HDF in both pre and post dilution mode

Fig. 10.2 Snapshot screen I

The use of Surdial-X is not limited to Nipro dialyzers, which makes it a very flexible system. However, should the user prefer to couple the machine with Nipro's dialyzers, the offer includes two families of products: ELISIO™ and SUREFLUX™. The ELISIO™ is a synthetic, Polynephron™ based membrane. It is a membrane that can be used for all modern techniques like HF, HD and HDF, during which it gives good clearance levels of small, middle and high molecular weight molecules keeping the amount of albumin leaching within acceptable limits [1]. The SUREFLUX™ dialyzer has a natural based membrane made of cellulose triacetate, making it one of the preferred membranes for sensitive and allergic patients. The use of cellulose triacetate membranes has become increasingly important due to the rising numbers of patients having an allergic response against synthetic membranes [2–4].

All Nipro dialyzers are di(2-ethylhexyl)phthalate (DEHP) free and additionally bisphenol A (BPA) free. If BPA is present in the dialyzers, either in fiber and/or housing, it has been shown to leach from them [5]. BPA is a known endocrine disruptor, which is associated with increased prevalence of albumin leakage in urine [6] and cardiovascular complications [7] in humans.

Bloodlines are specifically designed for the Surdial-X, allowing functions like the machine-assisted insertion of the pump segments or the automatic selection of the treatment mode. The HDF treatments rely on specific bloodline components including tubes for the pre and post dilution. Nipro offers HDF lines for either standard or single needle treatments. The Nipro portfolio also includes endotoxins retention filters for ultra-pure dialysate fluid.

Additional Programs and Options

The Surdial-X comes standard with two innovative techniques: Clean Treatment Start (CTS) and Dialysate Infusion Function (DIF).

- Clean treatment Start (CTS): permits the patient connection to the dialysis machine without infusing the priming solution into the patient; moreover, there is no need for an external drain bag, because the Surdial-X itself is used as a drain port to safely discard the fluid present in the blood lines after the priming. This is beneficial to patients with high blood pressure or high weight gain in the intra-dialytic period, as well as to nurses (avoiding the use of drain bags and the risks related to possible contact with blood) and administrators (escaping the cost of drain bags and related waste management).
- Dialysate Infusion Function (DIF) is a Surdial-X feature that allows the use of the typical online functions (machine priming, bolus administration and patient reinfusion) even without using the HDF circuit. Consequently, the advantages and the benefits of these functions are extended also to regular HD treatments.

Furthermore, in addition to the standard functionalities, extra options can be added. A second screen snapshot is shown in Fig. 10.3.

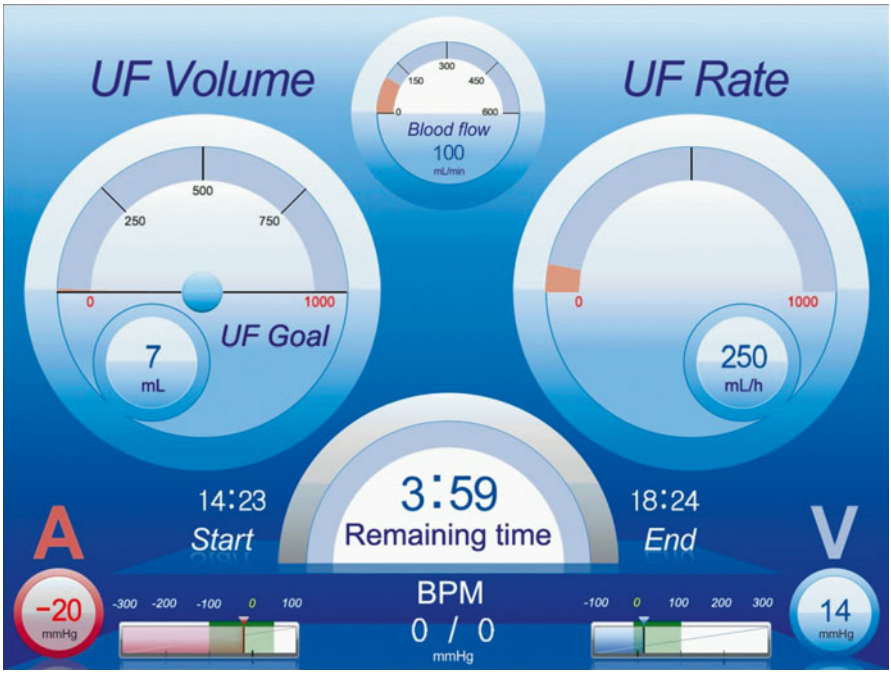


Fig. 10.3 Snapshot screen II

Additional Monitoring Options

The Surdial-X can integrate an advanced system for Blood Pressure Monitoring (BPM). The system keeps monitored the blood pressure parameters of the patient (Systolic, Diasystolic, MAP, Pulse) at intervals that can be customized by the user. Furthermore, the patient himself can activate, by remote control, extra measurements in case of need.

BPM function permits to set alarm ranges for the above mentioned blood pressure parameters. In case the value of BPM goes out of a preset range, the system alarms and, thanks to an internal feed-back, treatment's Ultra Filtration Rate and Blood Flow turn into pre-set values automatically.

Cleaning and Disinfection

Before each online HDF treatment, the unit has to be heat-disinfected with citric acid, or a chemical disinfection with sodium hypochlorite has to be done. Concentrations of the disinfection solution are properly specified on the unit's instruction manual, as well as all important technicalities related to cleaning and disinfection. The compact design of the hydraulics of the Surdial-X permits an extremely limited disinfection time: for example, a minimum of 29 minutes is required for hot citric cycle in HD.

Risk Management System

The Surdial-X is classified as class IIb according to 93/42/EEC Medical Device Directive and is equipped with all necessary safety features required for the performance and patient security. Safety features include arterial/venous pressure monitoring, arterial/venous clamps, bubble and blood leakage detectors, temperature monitoring, conductivity monitoring. A blood pump monitor acts as a protective system in case of blood coagulation in the blood line, triggering an alarm to assure patient safety. An alarm buzzer and a three-color light indicator promptly inform the user in case of malfunctioning. The safety control can be limited up to once every 24 months; maintenance every 24 months.

Display of Settings and Connection to Hospital Information System

All the settings of the Surdial-X are visualized on the touch screen, showing all parameters related to the operating mode, treatment and reinfusion processes, cleaning and disinfection, management of alarms. Regarding the connection to hospital

information system, the Surdial-X has networking capability, permitting the transmission of treatment data from the machine to the network. Export of data to an external software can be done with .XML or .HL7 files.

Cost Assessment

In terms of costs, the Surdial-X in HDF configuration requires the presence of two cut filters to assure the needed purity of the dialysis fluid, as previously implied. Besides this, specific bloodlines for HDF are required when the machine is used in such modality. The online functionality, however, permits to avoid the use of external saline solution; on the Surdial-X this possibility is not reserved to HDF configuration, but also feasible on HD versions thanks to the standard DIF function. For these reasons, a specific cost analysis is recommendable on a case-by-case basis, according to the system's configuration and the treatments planned by the clinic.

References

1. Meert N, Eloot S, Schepers E, et al. Comparison of removal capacity of two consecutive generations of high-flux dialysers during different treatment modalities. Nephrol Dial Transplant. 2011;26:2624–30.
2. Sánchez-Villanueva RJ, González E, Quirce S, et al. Hypersensitivity reactions to synthetic haemodialysis membranes. Nefrologia. 2014;34:520–5.
3. Martín-Navarro JA, Gutiérrez-Sánchez MJ, Petkov-Stoyanov V. Hypersensitivity to synthetic hemodialysis membranes. Nefrologia. 2014;34:807–78.
4. Olafiranye F, Kyaw W, Olafiranye O. Resolution of dialyzer membrane-associated thrombocytopenia with use of cellulose triacetate membrane: a case report. Case Rep Med. 2011;2011:134295.
5. Murakami K, Ohashi A, Hori H, et al. Accumulation of bisphenol A in hemodialysis patients. Blood Purif. 2007;25:290–4.
6. Trasande L, Attina TM, Trachtman H. Bisphenol A exposure is associated with low-grade urinary albumin excretion in children of the United States. Kidney Int. 2013;83:741–8.
7. Gao X, Wang HS. Impact of bisphenol A on the cardiovascular system – epidemiological and experimental evidence and molecular mechanisms. Int J Environ Res Public Health. 2014; 11:8399–413.

Part III
Effects of Hemodiafiltration on Various Biomarkers

Chapter 11
Effects of Convective Dialysis Techniques on Electrolytes and Mineral Metabolism

Andrew Davenport and Marc Vervloet

Abstract During hemodiafiltration, a large amount of substitution fluid, which has the same electrolyte and buffer concentration as the dialysate, is infused into the patients. Since the composition of the dialysis fluid is considerable different from the blood, bidirectional transmembrane exchanges occur which affect the final balance of vital anions and cations. These dynamics are greatly influenced by both the site of the infusion, i.e. before, halfway or after the dialyzer, and the magnitude of the convection volume. The current chapter describes the effect of hemodiafiltration on a variety of small molecular weight substances, such as sodium, potassium, calcium, magnesium, bicarbonate, chloride, phosphate and acetate. In addition, the influence of hemodiafiltration on some of the key parameters involved in CKD-MBD, including vitamin D, parathyroid hormone and fibroblast growth factor 23, is discussed.

Keywords Electrolytes • Sodium • Potassium • Magnesium • Bicarbonate • Chloride • Phosphate • Acetate • Vitamin D • Parathyroid hormone • FGF23 • CKD-MBD

Sodium

Sodium is a small positively charged cation. Besides covalent binding, sodium will also bind electrostatically to negatively charged proteins and lipids and as such there is a difference between the absolute sodium concentration in serum and that reported by standard laboratory potentiometry methods which determine sodium activity. Thus, as blood passes through a dialyzer, only that sodium which is freely available

A. Davenport, MD
UCL Centre for Nephrology, Royal Free Hospital, London, UK

M. Vervloet, MD, PhD (✉)
Department of Nephrology, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081 HV, The Netherlands
e-mail: m.vervloet@vumc.nl

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_11

to diffuse will cross the dialyzer membrane into dialysate if there is a positive gradient between serum sodium activity and that in the dialysate. As such sodium chemically or electrically bonded to other molecules is not freely available for diffusion. In addition, diffusion of molecules must maintain electrical neutrality (Gibbs-Donnan effect). On the other hand, during convection sodium can move across the dialyzer membrane with convective plasma water movement, which includes "free" sodium but also sodium bound to small molecular weight complexes. During extracorporeal therapies, the dialyzer membrane surface becomes coated with proteins. As such, sodium movement is then reduced by binding to proteins in this dialyzer membrane boundary layer. Thus, the amount of sodium in the ultrafiltrate will be slightly lower than that in plasma water [1]. The sieving coefficient (the ratio of ultrafiltrate to serum concentration) varies with predilution compared to postdilution haemofiltration, due to the diluting effect of infusing fluid and differences in membrane protein deposition. Although the difference in sieving coefficient appears small (Fig. 11.1), this will potentially make a difference in sodium balance when large volumes of fluid are exchanged (Fig. 11.2). The site of the replacement fluid has a much greater potential effect on the sodium balance compared to the replacement/substitution fluid sodium concentration [2].

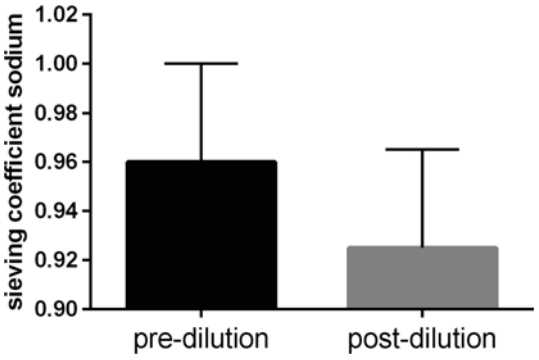


Fig. 11.1 Difference in sieving coefficient for sodium (ratio of ultrafiltrate to plasma sodium concentrations) in ten patients treated by pre compared to postdilution mode isovlaemic haemofiltration at an ultrafiltration rate of 100 ml/min

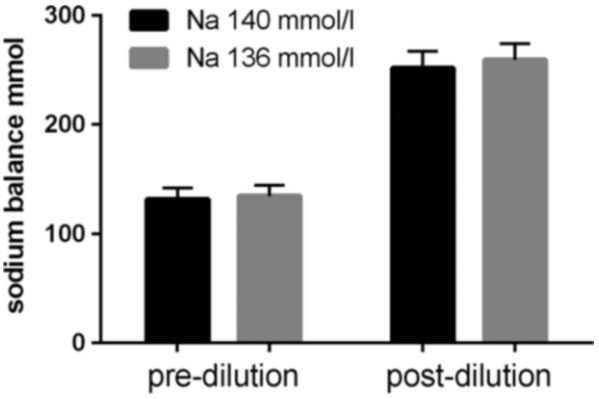


Fig. 11.2 Difference in net sodium balance sodium comparing pre to postdilution mode in ten patients with isovolaemic haemofiltration at an ultrafiltration rate of 100 ml/min. Mean and standard deviation

HDF combines both convective and diffusive clearance [3]. The convective element reduces net diffusion, particularly with the predilution mode by diluting solute concentrations. Depending upon the gradient between dialysate and serum sodium concentrations, sodium may be additionally lost or gained by diffusion [4]. Pedrini proposed a formula to estimate sodium changes with different forms of dialysis to account for different predialysis plasma sodium concentrations and different plasma to dialysate sodium gradients [5]. Acetate free hemodiafiltration or biofiltration (AFB), in which a bicarbonate free dialysate is used in combination with postdilution infusion of sodium bicarbonate, leads to a greater predicted positive sodium balance, followed by postdilution HDF with lower convective exchange volumes (Fig. 11.3). In theory, high volume postdilution HDF would be predicted to lead to an increased positive sodium balance compared to standard bicarbonate haemodialysis (HD), as larger convective volumes will increase protein deposition on the dialyzer membrane surface so increasing the charged protein polarisation boundary layer and so restricting sodium movement from the plasma water into the ultrafiltrate by reducing the sieving coefficient.

Although convective modes appear to result in a positive sodium balance, it must be recognised this relates to isovolaemic treatments [6], whereas in standard clinical practice most patients gain weight between treatment sessions and so will require ultrafiltration, which will result in a net overall sodium loss. However, HDF treatments, particularly when operated in the postdilution mode, are more likely to lead to a positive sodium balance than equivalent predilution HDF treatments (Fig. 11.4) [5], and this needs to be considered when choosing a sodium concentration for a given on-line HDF modality. In clinical practice, when patients are switched from standard haemodialysis to haemodiafiltration, a lower dialysate sodium concentration should be selected.

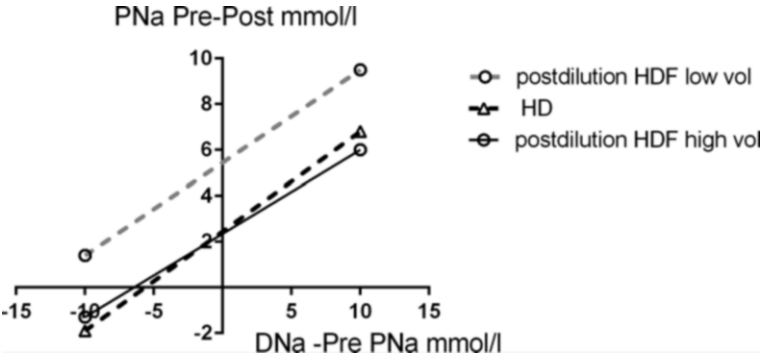


Fig. 11.3 Theoretical predictive differences in sodium balance based on the Pedrini equation [5] between haemodialysis and haemodiafiltration treatments, for a range of different dialysate (Dsodium) to plasma (Psodium) sodium gradients

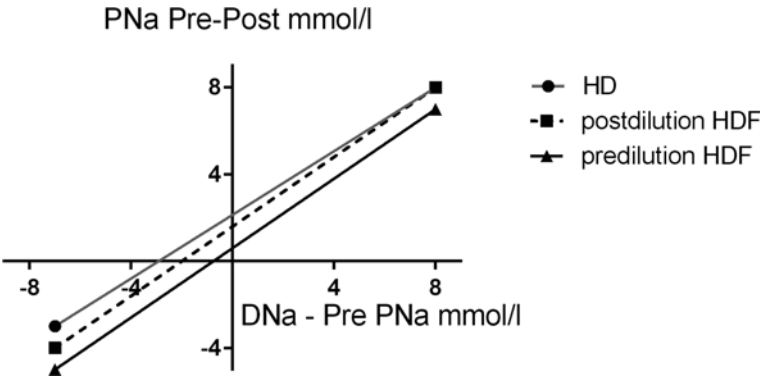


Fig. 11.4 Theoretical predictive differences in sodium balance based on the Pedrini equation [5] between pre and postdilution modes of haemodiafiltration treatments, for a range of different dialysate (Dsodium) to plasma (Psodium) sodium gradients

Potassium

Potassium is a small positively charged cation that is rapidly cleared during HD, as clearance is predominantly by diffusion. As with sodium, the sieving coefficient of potassium for convective clearance is less than one [6], and similarly the sieving coefficient is slightly higher for predilution HDF compared to the postdilution mode [2]. Compared to hemodialysis, less potassium will be removed by pure convective treatments. Although the sieving coefficient of potassium is higher with predilution, as the replacement/substitution fluids contain a much lower potassium concentration than the serum, the diluting effect of predialyzer fluid administration results in a lower potassium clearance compared to postdilution mode. Although HDF adds a diffusive element to potassium clearance, the convective clearance reduces the diffusive potassium clearance during passage through the dialyzer, and as such reduces potassium loss. As such, HDF, particularly in the predilution mode, is not as effective in total potassium removal compared to HD [7]. Meanwhile, the changes in electrocardiography QTc intervals, QRS dispersion and supraventricular premature beats depend more on the gradient between plasma and dialysate concentrations, rather than dialysis mode [8, 9], and, as with HD, modelling of potassium in the dialysate to minimise the potassium gradient reduces the risk of arrhythmias during HDF [10].

Although potassium removal during HDF is not affected by dialysate sodium concentration, the post-treatment rebound in plasma potassium is faster and greater when a positive sodium gradient (dialysate to plasma sodium) has been used compared to a negative sodium gradient [11].

Calcium

Extracorporeal calcium clearance is more complex than that of sodium and potassium due to greater protein binding of calcium. Approximately 40 % of serum calcium is bound, predominantly to albumin, but also to other negatively charged proteins and solutes. The equilibrium dynamic between free and bond calcium is not only affected by albumin concentration but also pH. Thus, when considering calcium clearance during extracorporeal therapies, changes in serum bicarbonate and pH have to be considered. Due to protein binding, the sieving coefficient for calcium is lower than that for sodium and potassium (Fig. 11.5). The difference in calcium mass transfer between predilution and postdilution modes is greater for calcium compared to sodium and potassium, as the calcium concentration of the replacement/ substitution fluids is typically higher than serum ionised calcium [2]. As such, with isovolaemic higher convection treatments (no net ultrafiltration) then net calcium balance becomes more positive with postdilution mode [2, 12] (Fig. 11.6). Although calcium balance will also depend upon the calcium

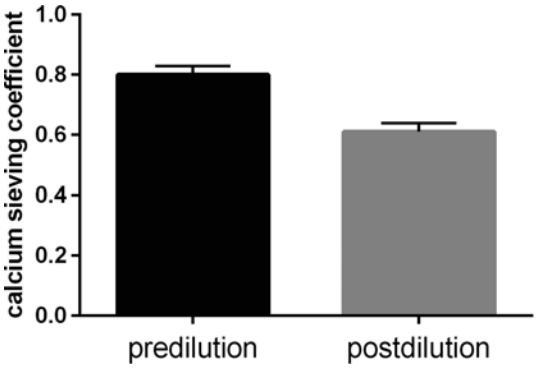


Fig. 11.5 Difference in sieving coefficient for calcium (ratio of ultrafiltrate to plasma calcium concentrations) in ten patients treated by pre compared to postdilution mode isovlaemic haemofiltration at an ultrafiltration rate of 100 ml/min

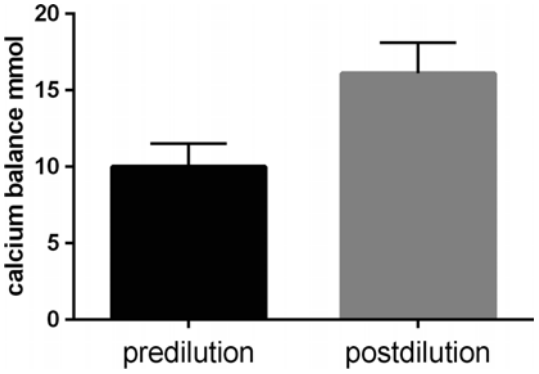


Fig. 11.6 Difference in net calcium balance comparing pre to postdilution mode in ten patients with isovlaemic haemofiltration at an ultrafiltration rate of 100 ml/min. Mean and standard deviation

composition of the replacement/substitution fluids, as with sodium, the infusion site of replacement/substitution fluids has a potentially greater effect on calcium balance [13]. Although some calcium will be removed by net ultrafiltration, most patients will be in a positive calcium balance when treated with convective techniques, and this accounts for the reports of lower PTH and greater response to calcifediol in patients treated by HDF [14].

Although adding a diffusive clearance with HDF will alter calcium balance depending upon the gradient between the respective dialysate and serum ionised concentrations, convective clearance of calcium has a greater effect on net calcium balance [15]. Predilution mode will have the least effect on diffusive clearance. Depending upon the calcium concentration chosen, administration of fluid in predilution mode will either increase or reduce the ionised plasma calcium concentration entering the dialyzer, but as the same calcium concentration is present in both the dialysate and replacement/substitution fluids, this will minimise the differential calcium gradient, between calcium entering the hemofilter and calcium in the dialysate. The gradient for diffusion will potentially be greater in postdilution mode [13]. As such, calcium mass transfer in HDF is also affected by the infusion mode. For a given concentration gradient between blood and dialysate, calcium balance in low volume post-dilution HDF may be similar to conventional HD [15], or positive, depending upon the amount of ultrafiltration [16]. Thus some clinicians have suggested to lower the dialysate calcium concentration during postdilution HDF to reduce the risk of a positive calcium balance [12].

As net calcium balance could be negative in the pre-dilution mode, especially with higher ultrafiltration rates and targeted weight loss, it has been suggested that the dialysate calcium concentration should be increased by approximately 0.25 mmol/l to maintain a comparable balance, when switching treatment from HD to pre-dilution HDF [15].

When choosing a dialysate calcium concentration for HDF, ideally this should be prescribed taking into consideration both the predicted HDF dialysis calcium mass balance, and the other concomitant therapies (calcium containing medications, vitamin D analogues) and the underlying type of mineral bone disease.

Magnesium

Magnesium, similar to calcium, has significant plasma protein binding, with some 40–50 % protein bound. As magnesium is widely present in the diet, healthy dialysis patients are more likely to develop hypermagnesaemia, and as such most dialysate and replacement/ substitution fluids contain equivalent normal or low ionised levels of magnesium [12]. Magnesium has a similar sieving coefficient to calcium, and as the replacement/substitution fluids have an equivalent magnesium concentration to the plasma ionised magnesium, predilutional modes may result in a negative magnesium balance, whereas postdilutional convective modes will potentially result in a positive magnesium balance [6].

The difference between calcium and magnesium balance is that most centres use a standard dialysate magnesium concentration of 0.5 mmol/l, which is around the lower limit of the normal plasma ionised magnesium concentration of 0.55–0.75 mmol/l, whereas on the other hand most dialysate calcium concentrations have a relatively high ionised dialysate calcium concentration of ≥1.0–1.25 mmol/l compared to the plasma ionised calcium concentration of 1.1–1.4 mmol/l [17]. As such, there is usually diffusive loss of magnesium during conventional HD. Adding a diffusive clearance with HDF may reduce diffusive losses in predilutional mode by diluting down the concentration gradient, and on the other hand increase diffusional losses in the postdilutional mode. However as with calcium, convection plays a greater role in determining magnesium balance. Predilution leads to greater convective losses, which increase with higher convection volumes [2].

Bicarbonate

Bicarbonate is a small negatively charged anion which requires transport across cell membranes, yet due to the protein boundary layer deposited on the dialyzer surface readily passes across the dialyzer, with a slight positive sieving coefficient. As such the sieving coefficient is greater in predilutional mode compared to postdilution [18]. Most replacement/substitution fluids contain supraphysiological levels of bicarbonate, and those for HDF will also contain a small amount of acetate, to prevent calcium carbonate deposition [19]. Predilution convection will result in less overall base accumulation [20], as there will be increased convective losses of both bicarbonate and acetate compared to the postdilution mode. Infusion of bicarbonate into the plasma leads to an increase in plasma pH, which then results in both an increased influx of calcium into cells and also increased plasma protein binding, so increasing the overall net calcium balance.

Bicarbonate moves rapidly from dialysate into plasma by diffusion down a concentration gradient. As such, adding a diffusional element with HDF improves correction of acidosis compared to pure convection techniques. Although in theory predilution by reducing the concentration gradient could potentially reduce the net bicarbonate influx compared to postdilution mode, in clinical practice there is no discernible difference between pre- and postdilution modes due to the predominance of diffusive bicarbonate movement compared to that of convective transport [21].

Chloride

As with bicarbonate, the sieving coefficient for chloride convection is just above one with predilution HDF and falls slightly with post-dilution [2]. Although most chloride concentrations for HD dialysates are around 110 mmol/l, commercially available replacement/substitution fluids for continuous forms of hemofiltration and

hemodiafiltration have a wide range of concentrations from 105 to 115 mmol/l. Depending upon the relative difference between serum and HDF replacement/substitution fluids, chloride balance may be negative or positive [6, 20]. The use of replacement fluids with lower concentrations of chloride increase the incidence of hypochloraemia, but improve the correction of metabolic acidosis, whereas higher chloride replacement solutions may lead to hyperchloraemia and metabolic acidosis. For the same chloride concentration predilution will tend to reduce chloride losses compared to postdilution [22].

As with bicarbonate, chloride quickly diffuses across the dialyzer membrane during HDF. Although in theory predilution HDF mode will reduce any chloride gains and losses in hypochloraemic and hyperchloraemic patients respectively, compared to postdilution mode, in clinical practice chloride balance is predominantly determined by diffusion. Most commercially available dialysate fluids contain a chloride of 110 mmol/l, and this will determine net chloride gains and losses during a treatment session [21].

Phosphate

Although phosphate is a relatively small molecule, due to its charges it has a larger water shell and so moves somewhat slower, such that whereas urea concentration in a red blood cell will fall during the time it takes to pass through the dialyzer, phosphate will not. As phosphate is predominantly intracellular, phosphate clearance by extracorporeal therapies is limited by the rate of movement from intracellular stores into plasma water, rather than by clearance from plasma water [23]. As replacement/substitution fluids for hemofiltration or hemodiafiltration traditionally contain no phosphate, more phosphate is cleared with higher convection volumes [24] and postdilutional convective therapies clear more phosphate than predilution modes. Similarly, as dialysates do not contain phosphate, adding a diffusional clearance with HDF, then more phosphate is cleared by diffusion than convection [25]. This diffusional element is lower in the predilutional mode as compared to postdilution HDF, and also reduced with increasing haematocrit [25]. Several observational studies have reported that serum phosphate concentrations are lower when switching patients from HD to HDF, or comparing cohorts of HDF to HD patients with similar small solute clearance [26, 27]. In clinical trials, predialysis phosphate levels either did not differ between patients treated with online postdilution hemodiafiltration or (mainly) high-flux hemodialysis [28, 29], or was slightly but significantly lower in patients treated with postdilution HDF as compared to low-flux hemodialysis [30]. However it has to be remembered that serum phosphate is a composite of dietary phosphate intake, gastrointestinal binding with phosphate binders, residual renal clearance and dialyzer clearance.

Acetate

Dialysates and on-line infusion fluids are made by mixing treated potable water with acid and bicarbonate concentrates. The mixture then contains calcium and carbonate which can precipitate out within the dialysate circuitry in the haemodialysis machine. To prevent or minimise such precipitation, a small amount of acetate (3–4 mmol/l) is typically added to the dialysate. Historically in the 1960s–1980s standard dialysates for low flux haemodialysis contained acetate rather than bicarbonate as the anionic base. Although meta-analysis of randomised trials did not show an overall benefit for bicarbonate dialysate, several studies linked acetate based dialysates with a greater risk for intra-dialytic hypotension. During on-line HDF, re-infusion of an acetate containing fluid will lead to increased acetate delivery to the patient. Predilution fluid replacement will reduce acetate delivery compared to postdilution at similar infusion rates. There will also be an additional acetate influx due to the presence of acetate in the dialysate. During on-line HDF the serum acetate will typically be limited to around a maximum of 0.5 mmol/l [31], but this hides the fact that there is a net acetate flux, with acetate passing into cells. Alternatives to on-line HDF include HDF using pre-prepared sterile bags of substitution fluid, or acetate free biofiltration, in which a bicarbonate free dialysate is used in combination with reinfusion of sodium bicarbonate in postdilution mode [32]. Small studies have reported that acetate free treatments cause less leukocyte and monocyte activation and lower inflammatory cytokine releases [33]. However there have been no clinical studies showing any differences in intra-treatment cardiovascular stability or longer term nutritional or survival differences between acetate containing fluids and acetate free fluids for HDF [5, 34].

Teaching Points I

- High volume HDF may result in a net zero sodium balance, depending on the sodium concentration of the substitution fluid used
- The infusion site of both calcium and sodium has a greater effect on ionic balance than its concentrations in the substitution fluid
- High volume HDF may result in a positive calcium balance, depending on dialysate calcium concentration and prescribed medication
- Predilution HDF may lead to undesirable magnesium losses
- In HDF, both bicarbonate and chloride transport are mainly determined by diffusion
- As far as serum levels of phosphate are concerned, HDF offers no advantage over high-flux HD.

Vitamin D

Since the lipophylic vitamin D metabolites like cholecalciferol, calcitriol, and its catabolic products 24,25 dihydroxycholecalciferol and 1,24,25 $(OH)_3$ cholecalciferol are all nearly completely bound to Vitamin D Binding Protein (VDBP), their clearance by either diffusion or convection is negligible. Although in peritoneal dialysis some vitamin D may be lost in the dialysate, along with VDBP, this dialysis technique too does not lead to a clinically relevant decline in its plasma concentrations [35, 36]. Nevertheless, due to changes in calcium and phosphate homeostasis specifically induced by HDF techniques as described above, altered vitamin D levels could be induced by biological feedback systems. In addition, improved clearance by HDF of (yet unidentified) middle-molecules involved in vitamin D metabolism could change its levels.

Observational data do show indeed that online HDF is associated with higher 25(OH)D3 levels as compared to conventional HD [37]. Although no correction for potential differences in calcium balance was carried out, the presumed impact of calcium balance on this storage form of vitamin D is probably limited, and therefore this finding suggests either improved gastrointestinal uptake or cutaneous production of 25(OH)D3, or delayed catabolism during HDF. The clearance of fibroblast growth factor 23 (FGF23), a vitamin D catabolic hormone, is higher for HDF, see next paragraph [38]. However, this does not explain the higher levels of 25(OH)D3, as the assays used to detect this vitamin D compound do not differentiate 25(OH)D3 from its catabolic product $24,25(OH)_2D3$. FGF23 could however increase the ratio $24,25(OH)_2D3/25(OH)D3$, which may remain unnoticed due to the lack of specificity of the assay. Nevertheless, the observation that supplementation of non-active vitamin D to patients treated by on-line HDF induces a higher peak level than those treated by conventional HD does suggest a "vitamin D sparing effect" of the former technique, see Fig. 11.7 [14]. This assumption is also supported by the evo-

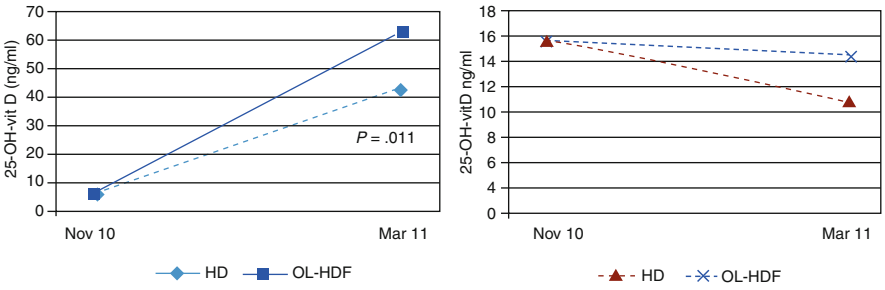


Fig. 11.7 Response to treatment with calcifediol. *Left panel*: Levels of 25(OH)vit D3 before and after 4 months of treatment with iv calcifediol (266 μg once a week after treatment) in 23 patients treated with high-flux hemodialysis and 13 patients treated with postdilution online hemodiafiltration. *Right panel*: Levels of 25(OH)vit D3 without supplementation during the same time frame in 15 patients treated with high-flux hemodialysis and 8 patients treated with postdilution online hemodiafiltration (Reprinted from Perez-Garcia et al. [14]. With permission from Revista Nefrología)

lution of 25(OH)D3 levels in non-supplemented patients in the two different dialysis modalities, showing a steeper decline for conventional HD [14].

Since the skin is the most important source of vitamin D by far, due to local production under the influence of UV-B light, a potentially important advantage of HDF may be the improvement of skin hyperpigmentation as compared to conventional HD [39]. This improvement is likely related to improved clearance of middle-molecules involved in regulation of melanin since this feature is also present in peritoneal dialysis [40]. The attenuated hyperpigmentation probably facilitates the penetration of UV-B light [41], although the hyperpigmentation in CKD may not be due solely to a melanin dependent mechanism.

Parathyroid Hormone (PTH)

PTH is a polypeptide hormone with a molecular weight of 9.4 kDa, and as such it classifies as a middle molecule. These properties predict improved dialysability of PTH in HDF and indeed this hormone can be detected in the dialysate, although the amounts of intact PTH are low [42]. The most important method of clearance appears to be adsorption onto the dialyser membrane and is dependent on the material of the membrane used [43]. At least when compared to high-flux HD, online HDF does not lead to increased clearance of PTH in either observational studies [44] or prospective randomized trials [29]. Based on its molecular weight, improved clearance during HDF over low-flux HD is likely, as high-flux HD, even after correcting for ionized calcium, leads to lower PTH concentrations than low-flux HD [45].

Besides direct increased clearance during HDF, this technique can influence PTH levels by modifying PTH secretion from the parathyroid glands. Several humoral factors are involved in PTH regulation, like calcium and phosphate concentrations, and active vitamin D and FGF23 levels. The latter two hormones are both inhibitors of PTH production and secretion, but their kinetics diverge during HDF. As vitamin D (at least 25(OH)D3) tends to increase and FGF23 tends to decline (see next paragraph), the net effect on PTH secretion may be balanced. As outlined above, HDF can impact calcium homeostasis in a complex fashion, depending not only on calcium concentrations in the dialysate and replacement fluids, but also on to the mode of HDF, i.e. predilution or postdilution. Since calcium is the single most important immediate regulator of PTH secretion, and its effects are swift [46], the consequences of HDF on PTH are to a large extent mediated by changes in either calcium concentration or balance. Furthermore, some clearance of PTH by absorption onto the dialyser membrane or filtration across highly permeable dialysers also occurs [43]. Indeed, targeting calcium balance directly by modifying calcium concentration in dialysate or replacement fluid directly affects PTH concentrations [47], and therefore, an overall decline in PTH can be anticipated during HDF. This also applies to children where a low calcium concentration of 1.25 mmol/l can be advised to prevent fracture risk due to PTH oversuppression when using calcium concentration of 1.5 mmol/l [48]. On the contrary, when a

replacement fluid not containing calcium is used, calcium balance will be negative and PTH will increase accordingly [49]. An optimal calcium concentration during HDF, defined by a neutral effect on PTH, is between 1.25 and 1.5 mmol/l [50].

Theoretically, in addition to calcium, differential effects of HDF as compared to conventional HD on phosphate concentrations or phosphate balance could impact PTH, as phosphate stimulates PTH, at least so in healthy subjects. However, as outlined in the previous section of this chapter, in contrast to observational studies or non-randomized trials [26, 27], well-designed prospective trials show no or only very limited enhanced phosphate clearance by HDF as compared to HD [29, 51, 52]. Therefore, altered clearance of phosphate during HDF probably does not induce meaningful changes in PTH.

In conclusion, during HDF a slight decline in PTH can be expected, as a consequence of increased clearance, absorption onto the membrane and a tendency for a slight positive calcium balance when using the same calcium concentration of the replacement solution as the dialysate in conventional HD. Given the increasing prevalence of adynamic bone disease in HD populations, and the association of that specific bone disease with dismal cardiovascular outcome, a slightly lower calcium concentration for the ultrapure dialysate and infusate during HDF could be considered.

Fibroblast Growth Factor 23 (FGF23)

Like PTH, FGF23 qualifies as a middle-molecule. As the molecular weight of the biological active compound is 32 kD and this polypeptide is hydrophilic, theoretically increased clearance during HDF can be expected. Although the metabolic fate of FGF23 during end- stage renal disease is unclear, limited data point to diminished catabolism [53]. Therefore, the relative importance of renal replacement therapy in clearing this phosphate-regulating hormone may be of high importance, given the strong predictive power of high levels of FGF23 to all cause and cardiovascular mortality [54]. Despite the above-mentioned properties, FGF23 levels decline with more intensive low-flux HD schedules as well [55]. This observation can likely be explained by improved control of circulating factors of importance for FGF23 production, like phosphate itself. As predicted from its properties, HDF leads to a decline of FGF23 of 56 % percent from its value directly prior to the treatment session, as compared to a 36 % reduction during high-flux HD, pointing to the relative importance of convective clearance of this compound [38]. Likewise, in paediatric HDF, a substantial reduction of FGF23 was observed [48]. When compared to low-flux HD, clearance of FGF23 by HDF is even more impressive, with negligible decline during the former modality [56]. In a small subset of the prospective CONTRAST trial, comparing low-flux HD with HDF, the former technique led to a 10 % reduction of FGF23, while patients randomized to HDF had a decline of almost 50 % (Den Hoedt, ASN 2010 PO1436). Despite the striking consistency that exists among large observational studies showing strong independent associations between FGF23 and a range of clinically important outcomes measures, no

evidence yet has shown improved outcome when directly targeting FGF23 by either modifying dietary phosphate intake or the use of phosphate binder therapy. If FGF23 decline induced by high-volume HDF improves clinical outcome is currently unknown.

Teaching Points II

- In CKD, the level of vitamin D, which is highly protein bound, is decreased
- Due to its protein binding, vitamin D concentrations are hardly influenced by convective transport
- Since vitamin D levels increase after HDF, other mechanisms, such as changes vitamin D regulating factors, and attenuation of CKD-related hyperpigmentation, might play a role
- PTH is a MMW substance, which, on theoretical grounds, may be removed by convection. Yet, in large HDF studies, reductions in PTH were modest or absent compared to high-flux HD.
- FGF23, which has an even larger MW than PTH, is reduced by HDF up to 50 % of its initial value
- Currently, data showing an association between reductions in both FGF23 and mortality are lacking

References

1. Shaldon S. Role of small molecule removal in the control of treatment morbidity with haemodialysis and haemofiltration. Proc Eur Dial Transplant Assoc Eur Ren Assoc. 1981;18: 249–55.
2. Uchino S, Cole L, Morimatsu H, Goldsmith D, Ronco C, Bellomo R. Solute mass balance during isovolaemic high volume haemofiltration. Intensive Care Med. 2003;29:1541–6.
3. Gotch FA, Lam MA, Prowitt M, Keen M. Preliminary clinical results with sodium-volume modeling of hemodialysis therapy. Proc Clin Dial Transplant Forum. 1980;10:12–7.
4. Shaldon S, Baldamus CA, Beau MC, Koch KM, Mion CM, Lysaght MJ. Acute and chronic studies of the relationship between sodium flux in hemodialysis and hemofiltration. Trans Am Soc Artif Intern Organs. 1983;29:641–4.
5. Pedrini LA, De Cristofaro V, Pagliari B, Ruggiero P. Dialysate/infusate composition and infusion mode in on-line hemodiafiltration. Contrib Nephrol. 2002;137:344–9.
6. Tan HK, Uchino S, Bellomo R. Electrolyte mass balance during CVVH: lactate vs. bicarbonate-buffered replacement fluids. Ren Fail. 2004;26:149–53.
7. Severi S, Vecchietti S, Cavalcanti S, Mancini E, Santoro A. Electrocardiographic changes during hemodiafiltration with different potassium removal rates. Blood Purif. 2003;21:381–8.
8. Munoz RI, Montenegro J, Salcedo A, et al. Effect of acetate-free biofiltration with a potassium-profiled dialysate on the control of cardiac arrhythmias in patients at risk: a pilot study. Hemodial Int. 2008;12:108–13.
9. Coppolino G, Bolignano D, Parisi S, et al. Experimental therapies in renal replacement: the effect of two different potassium acetate-free biofiltration protocols on striated muscle fibers. Ther Apher Dial. 2007;11:375–81.
10. Buemi M, Aloisi E, Coppolino G, et al. The effect of two different protocols of potassium haemodiafiltration on QT dispersion. Nephrol Dial Transplant. 2005;20:1148–54.

11. De Nicola L, Bellizzi V, Minutolo R, et al. Effect of dialysate sodium concentration on interdialytic increase of potassium. J Am Soc Nephrol. 2000;11:2337–43.
12. Severi S, Bolasco P, Badiali F, et al. Calcium profiling in hemodiafiltration: a new way to reduce the calcium overload risk without compromising cardiovascular stability. Int J Artif Organs. 2014;37:206–14.
13. Karamperis N, Jensen D, Sloth E, Jensen JD. Comparison of predilution hemodiafiltration and low-flux hemodialysis at temperature-controlled conditions using high calcium-ion concentration in the replacement and dialysis fluid. Clin Nephrol. 2007;67:230–9.
14. Perez-Garcia R, Albalate M, de Sequera P, et al. On-line haemodiafiltration improves response to calcifediol treatment. Nefrologia. 2012;32:459–66.
15. Malberti F, Ravani P. The choice of the dialysate calcium concentration in the management of patients on haemodialysis and haemodiafiltration. Nephrol Dial Transplant. 2003;18 Suppl 7:vii37–40; discussion vii57.
16. Floccari F, Aloisi E, Nostro L, et al. QTc interval and QTc dispersion during haemodiafiltration. Nephrology. 2004;9:335–40.
17. Vitale C, Marangella M, Ramello A. Dialysate/infusate calcium and magnesium. Contrib Nephrol. 2002;137:350–6.
18. Sternby JP, Nilsson A, Garred LJ. Diffusive-convective mass transfer rates for solutes present on both sides of a dialyzer membrane. ASAIO J. 2005;51:246–51.
19. Hernandez-Jaras J, Garcia H, Ferrero JA. Changes in the anion gap in patients undergoing hemodiafiltration. Nefrologia. 2000;20:66–71.
20. Cole L, Bellomo R, Baldwin I, Hayhoe M, Ronco C. The impact of lactate-buffered high-volume hemofiltration on acid-base balance. Intensive Care Med. 2003;29:1113–20.
21. Ahrenholz P, Winkler RE, Ramlow W, Tiess M, Thews O. On-line hemodiafiltration with pre- and postdilution: impact on the acid-base status. Int J Artif Organs. 1998;21:321–7.
22. Davenport A, Worth DP, Will EJ. Hypochloraemic alkalosis after high-flux continuous haemofiltration and continuous arteriovenous haemofiltration with dialysis. Lancet. 1988;1:658.
23. Spalding EM, Chamney PW, Farrington K. Phosphate kinetics during hemodialysis: evidence for biphasic regulation. Kidney Int. 2002;61:655–67.
24. Troyanov S, Cardinal J, Geadah D, et al. Solute clearances during continuous venovenous haemofiltration at various ultrafiltration flow rates using multiflow-100 and HF1000 filters. Nephrol Dial Transplant. 2003;18:961–6.
25. Spalding EM, Pandya P, Farrington K. Effect of high haematocrit on the efficiency of high-flux dialysis therapies. Nephron Clin Pract. 2008;110:c86–92.
26. Movilli E, Camerini C, Gaggia P, et al. Effect of post-dilutional on-line haemodiafiltration on serum calcium, phosphate and parathyroid hormone concentrations in uraemic patients. Nephrol Dial Transplant. 2011;26:4032–7.
27. Davenport A, Gardner C, Delaney M, Pan Thames Renal Audit G. The effect of dialysis modality on phosphate control: haemodialysis compared to haemodiafiltration. The Pan Thames Renal Audit. Nephrol Dial Transplant. 2010;25:897–901.
28. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
29. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28:192–202.
30. Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
31. Pizzarelli F, Cerrai T, Dattolo P, Ferro G. On-line haemodiafiltration with and without acetate. Nephrol Dial Transplant. 2006;21:1648–51.
32. Santoro A, Ferrari G, Spongano M, Badiali F, Zucchelli P. Acetate-free biofiltration: a viable alternative to bicarbonate dialysis. Artif Organs. 1989;13:476–9.
33. Todeschini M, Macconi D, Fernandez NG, et al. Effect of acetate-free biofiltration and bicarbonate hemodialysis on neutrophil activation. Am J Kidney Dis. 2002;40:783–93.
34. Pizzarelli F, Cerrai T, Dattolo P, Tetta C, Maggiore Q. Convective treatments with on-line production of replacement fluid: a clinical experience lasting 6 years. Nephrol Dial Transplant. 1998;13:363–9.

35. Joffe P, Heaf JG. Vitamin D and vitamin-D-binding protein kinetics in patients treated with continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int. 1989;9:281–4.
36. Prytula A, Wells D, McLean T, et al. Urinary and dialysate losses of vitamin D-binding protein in children on chronic peritoneal dialysis. Pediatr Nephrol. 2012;27:643–9.
37. Gracia-Iguacel C, Gallar P, Qureshi AR, et al. Vitamin D deficiency in dialysis patients: effect of dialysis modality and implications on outcome. J Ren Nutr. 2010;20:359–67.
38. Patrier L, Dupuy AM, Granger Vallee A, et al. FGF-23 removal is improved by on-line high-efficiency hemodiafiltration compared to conventional high flux hemodialysis. J Nephrol. 2013;26:342–9.
39. Shibata M, Nagai K, Usami K, Tawada H, Taniguchi S. The quantitative evaluation of online haemodiafiltration effect on skin hyperpigmentation. Nephrol Dial Transplant. 2011;26: 988–92.
40. Lai CF, Kao TW, Tsai TF, et al. Quantitative comparison of skin colors in patients with ESRD undergoing different dialysis modalities. Am J Kidney Dis. 2006;48:292–300.
41. Shoenfeld N, Amital H, Shoenfeld Y. The effect of melanism and vitamin D synthesis on the incidence of autoimmune disease. Nat Clin Pract Rheumatol. 2009;5:99–105.
42. De Francisco AL, Amado JA, Prieto M, et al. Dialysis membranes and PTH changes during hemodialysis in patients with secondary hyperparathyroidism. Nephron. 1994;66:442–6.
43. Balducci A, Coen G, Manni M, et al. In vivo assessment of intact parathyroid hormone adsorption by different dialysis membranes during hemodialysis. Artif Organs. 2004;28: 1067–75.
44. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009;4:1944–53.
45. Makar SH, Sawires HK, Farid TM, Ali WM, Schaalan M. Effect of high-flux versus low-flux dialysis membranes on parathyroid hormone. Iran J Kidney Dis. 2010;4:327–32.
46. Messa P, Vallone C, Mioni G, et al. Direct in vivo assessment of parathyroid hormone-calcium relationship curve in renal patients. Kidney Int. 1994;46:1713–20.
47. Jean G, Mayor B, Hurot JM, et al. Biological impact of targeted dialysate calcium changes in haemodialysis patients: the key role of parathyroid hormone. Nephrol Dial Transplant. 2013;28:176–82.
48. Perouse de Montclos T, Ranchin B, Leclerc AL, et al. Online hemodiafiltration in children and hypoparathyroidism: a single-centre series of cases. Nephrol Ther. 2014;10:35–8.
49. Rius A, Hernandez-Jaras J, Pons R, et al. Kinetic of calcium, phosphate, magnesium and PTH variations during hemodiafiltration. Nefrologia. 2007;27:593–8.
50. Argiles A, Mourad G, Lorho R, et al. Medical treatment of severe hyperparathyroidism and its influence on anaemia in end-stage renal failure. Nephrol Dial Transplant. 1994;9:1809–12.
51. Locatelli F, Altieri P, Andrulli S, et al. Phosphate levels in patients treated with low-flux haemodialysis, pre-dilution haemofiltration and haemodiafiltration: post hoc analysis of a multicentre, randomized and controlled trial. Nephrol Dial Transplant. 2014;29:1239–46.
52. Penne EL, van der Weerd NC, van den Dorpel MA, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55:77–87.
53. Shimada T, Urakawa I, Isakova T, et al. Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. J Clin Endocrinol Metab. 2010;95:578–85.
54. Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359:584–92.
55. Zaritsky J, Rastogi A, Fischmann G, et al. Short daily hemodialysis is associated with lower plasma FGF23 levels when compared with conventional hemodialysis. Nephrol Dial Transplant. 2014;29:437–41.
56. Miao LY, Zhu B, He XZ, et al. Effects of three blood purification methods on serum fibroblast growth factor-23 clearance in patients with hyperphosphatemia undergoing maintenance hemodialysis. Exp Ther Med. 2014;7:947–52.

Chapter 12
Effects of Haemodiafiltration of Anemia Control

Lucia Del Vecchio, Neelke C. van der Weerd, and Francesco Locatelli

Abstract Anaemia secondary to chronic kidney disease is a complex syndrome. Adequate dialysis can contribute to its correction by removing small, and possibly medium/large toxins that inhibit erythropoiesis. Accordingly, a positive relationship between anaemia improvement and dialysis dose has already been observed in the 1980s. Dialysate contamination and low-compatible treatments may also increase cytokine production and consequently inhibit erythropoiesis. Convective treatments and, particularly, on-line haemodiafiltration, could theoretically improve anaemia correction by two mechanisms: higher removal of medium and large solutes (possibly containing bone marrow inhibitors) and reduced microbiological and pyrogenic contamination of the dialysate. Unfortunately, available results are conflicting, mainly because of differences in treatment modalities or membranes, and lack of control groups. Patient selection and higher achieved dialysis dose with online hemodiafiltration may also have complicated interpretation. Increasing treatment time (nocturnal dialysis) and/or frequency (daily dialysis) may diminish rebound from the extravascular space of middle- large molecules and thus possibly improve anaemia. Again, available studies are conflicting.

Keywords Chronic kidney disease • Anaemia • Dialysis • Erythropoiesis stimulating agents • Inflammation • On-line haemodiafiltration • Adequacy • Iron • Hepcidin

L. Del Vecchio, MD • F. Locatelli, MD (✉)
Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy
e-mail: f.locatelli@ospedale.lecco.it

N.C. van der Weerd, MD, PhD
Division of Nephrology, Department of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_12

Introduction

Anaemia is a common complication of chronic kidney disease (CKD), affecting the majority of patients on dialysis. Traditionally, renal anaemia is treated by the administration of erythropoiesis stimulating agents (ESA), iron administration and blood transfusions in selected cases. Despite the fact that these strategies are available for decades, there are still many "grey areas", such as the optimal haemoglobin (Hb) target concentration and concerns about the general safety of ESA and iron supplementation. In particular, clinical trials investigating the role of complete anaemia correction with ESA have shown an increased risk of thromboembolic events (in particular stroke) and cancer-related death in the higher Hb target groups [1]. Currently, however, it is still unclear whether patient characteristics, such as comorbidities and inflammatory status, or treatment-related factors, including high ESA doses, expose patients to a higher risk of adverse events [2]. ESA hyporesponsiveness appears important, since for every range of achieved Hb levels, a higher ESA dose [erythropoiesis resistance index (ERI)] was associated with an unfavourable outcome [3, 4]. Moreover, irrespective of the achieved Hb concentration, those treated with the highest ESA doses had a significantly higher relative risk for the primary end point [5], indicating that the ESA dose and not the achieved Hb was the principal determinant of clinical outcome. However, ESA dose may be a marker of a higher comorbidity burden as well. Overall, any effort to reduce ESA requirements for a given Hb target could be of potential benefit.

Why Do Patients with Chronic Kidney Disease Develop Anaemia?

In CKD patients, the main factor causing anaemia is a reduced renal production of erythropoietin (EPO) by the failing kidneys, together with a resistance of the bone marrow cells to this hormone. The balance between the two conditions determines the severity of anaemia in the individual patient. Accordingly, some CKD patients may have near-to normal erythropoietin levels, which, however, are inadequate for the severity of anaemia. The presence of relative high endogenous EPO levels despite persisting anaemia is a marker of poor outcome [6], underlying the relative importance of factors that depress erythropoiesis.

The reduced erythropoiesis of CKD patients has several causes, including iron deficiency, chronic inflammation and oxidative stress. Causes of anaemia in CKD patients are summarised in Table 12.1.

Research from the 1960s already showed that toxic substances inhibiting erythropoiesis could be found in the serum of nephrectomised rabbits [7]. A number of metabolites or substances are potential uremic toxins, including various polyamines, such as spermine, spermidine, putrescine [8], cadaverine. High levels of parathyroid hormone can also worsen anaemia, although it may not specifically

Table 12.1 Factors contributing to anaemia in patients with chronic kidney disease

Low erythropoietin production (relative)
Absolute or functional iron deficiency
Vitamin B12/folate defiency
Shorter erythrocyte survival
Severe secondary hyperparathyroidism
Infections/chronic inflammation
Bleeding
Inadequate dialysis
Malnutrition
Frequent blood sampling
Blood loss during dialysis

suppress erythropoiesis, but rather cause a fibrotic transformation of the bone marrow [9]. Polymeric polyamine-protein conjugates are more selective and accumulate during dialysis, suggesting a possible causative role of dialysis treatment per se [10].

Inflammatory cytokines can also inhibit erythropoiesis. Although available data are not unequivocal, interleukin-6 (IL-6) has been found to antagonize the effect of EPO on bone marrow proliferation [11]. Actually, IL-6 levels were directly related to the ESA dose [12] and significantly higher in patients treated with less compatible membranes [13]. Together with C-reactive protein (CRP), IL-6 appeared to be a strong and independent predictor of ERI in HD patients [14]. An inverse correlation between IL-6 and anaemia was observed also in CKD patients not yet on dialysis [15]. Other pro-inflammatory cytokines, including Interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and interferon-ϒ (IFN-ϒ) have been related as well to EPO resistance [16, 17]. The latter substances, however, act by different mechanisms, such as inducing a shortened red blood cell survival, abnormal mobilization of reticuloendothelial iron stores, blunted EPO response and impaired erythroid colony formation in response to EPO.

Uremic toxins originating from the gut may also negatively influence EPO synthesis. Quinolinic acid, which is the product of tryptophan oxidation by intestinal bacteria, can both suppress erythroid colony formation [18] and inhibit EPO production [19]. Indoxylsulfate, which accumulates early in CKD and exerts detrimental effects on the cardiovascular system, increases oxygen consumption in tubules and aggravates hypoxia in the kidney. Several data showed that indoxylsulfate suppresses EPO expression, which is partially mediated by a reduced induction of hypoxia-inducible factor (HIF)-1 target genes in the presence of hypoxia [20].

A concomitant shortened red blood cell survival may also play a role. Inflammation, increased oxidative stress and uremic toxins induce premature changes in the erythrocyte membrane and cytoskeleton, leading to exposition of phosphatidylserine at the cell surface and accelerated phagocytosis by macrophages. This phenomenon, called programmed cell death or eryptosis, is enhanced in CKD. Other uremic toxins, such as vanadate [21], acrolein [22], methylglyoxal [22], and indoxylsulphate [23] have been shown to trigger eryptosis as well.

Anaemia and Dialysis Dose

In 1980 it was already found that anaemia improved after the start of HD [24], which was then attributed to the removal of small molecules, which may inhibit erythropoiesis. If so, a higher dialysis dose, as indicated by Kt/V_{urea}, would improve anaemia. In the 1990s, Ifudu et al. [25] found a direct relationship between haematocrit and dialysis dose, which, however, could have been influenced by the concomitant shift from modified cellulose to high permeable and more biocompatible membranes in the patients previously receiving inadequate dialysis [26]. Later, in large cohort studies, a clear relationship between the degree of anaemia and dialysis dose was found [26, 27], although it was not completely clear whether anaemia control improved by the application of a different dialysis modality and/or by an improved dialysis dose. More recently, Movilli et al. [28] found an inverse relationship between ESA dose and Kt/V_{urea} in 68 patients on conventional HD, independent of membrane permeability and biocompatibility. In a larger cohort, this correlation was significant only in patients with Kt/V_{urea} below 1.33 [29]. Gaweda et al. [30] confirmed the observation that the relationship between dialysis dose and anaemia is not linear and vanishes when "adequate dialysis" (i.e. $Kt/V_{urea} > 1.4$) is obtained.

Convective Treatments

Convective treatments combine large pore membranes with a high trans-membrane flux. Thanks to these properties, theoretically, middle molecular weight (MMW) inhibitors of erythropoiesis are more easily removed. However, due to obligate back filtration in high-flux HD the amount of convective transport is unpredictable, immeasurable and fluctuates per treatment. Nevertheless, anaemia improvement had been observed after switching from standard HD to HD with high permeable and biocompatible membranes in several small and uncontrolled studies from the 1990s [31–34], and more recently in a small randomised study as well [35]. The Italian Cooperative Dialysis Study compared biocompatible and traditional dialyzers as well as convective and diffuse treatment modalities in 380 patients [36]. A secondary analysis showed a significant increase in haematocrit levels in patients on high-flux polysulphone (PS) HD and high-flux PS haemodiafiltration (HDF) compared to those on low-flux treatments (cuprophane HD, low-flux PS HD), but did not find any difference when all four groups were analysed separately. Hence, it is highly doubtful whether an increase in convective transport in the HDF group has influenced these findings [37]. Finally, one large, observational, cohort study from the Japanese phase II DOPPS [38], as well as two randomised, controlled trials [39, 40] failed to demonstrate an effect of high-flux HD on anaemia. Unfortunately, neither the Hemo-dialysis (HEMO) Study [41] nor the Membrane Permeability Outcome Study (MPO) study [42], which are the largest randomized clinical trials (RCT) that examined the effect of membrane flux and dialysis dose on clinical

outcomes, published data on anaemia control (although unpublished data of the MPO study do not suggest that high-flux was superior to low-flux in this respect).

Online Haemodiafiltration

Online HDF is probably the most efficient technique of removing solutes up to 50 kD. Since the dialysis fluid in this modality is obligatory ultrapure (bacterial contamination <0.1 CFU/ml, LAL <0.025 IU/ml), both high convection coupled with purity may constitute the rationale for an improvement of anaemia. Unfortunately, studies investigating the effects of HDF on anaemia and iron parameters, as well as on ESA dosing and iron supplementation differ considerably in design, patient numbers, control group and endpoints (Table 12.2). In most publications, anaemia management was a secondary endpoint, without providing information on iron parameters and iron supplementation. Lin et al. [43] switched 92 patients from conventional HD to on-line HDF and found a significant decrease of the median ESA/haematocrit ratio (from 504.6 ± 310.1 to 307.6 ± 334.4), which might, however, be also the result of a marked increase in Kt/V in this group. Bonforte et al. [44] studied 32 patients treated by on-line HDF for at least 9 months in whom the dialysis dose was kept constant. Despite the small sample size and the lack of a control group, a significant increase in Hb levels was found in patients without ESA therapy and stable Hb values and lower ESA doses in those patients who already received ESA therapy. Vaslaki et al. [45] performed a randomised, cross-over study in 70 patients receiving either HDF or conventional HD for 6 months. Overall, a higher haematocrit at a lower ESA dose was found during the HDF period, although these data were less distinct when considering separately the two groups undergoing HDF. Finally, two small, RCTs [46, 47] failed to demonstrate an effect of HDF on anaemia control, which may be due to an inadequate statistical power (a relative small sample size to test the difference between two efficient dialysis techniques).

To overcome the issue of small sample size, in 2013 a meta-analysis of 65 studies was performed (12,182 patients, only studies published before December 2012 included) comparing convective therapies (including high-flux HD, hemofiltration [HF] and HDF) with low-flux HD, which did not show an improved anaemia control nor a decreased ESA dose or improved iron parameters in patients treated with convective therapies [48]. After publication of this meta-analysis, several larger randomised studies have been published on this topic.

In 2012 a pre-specified secondary analysis of a multicentre, open-label, RCT of 146 CKD patients, who were randomized to standard HD (70 patients) or convective treatments (online pre-dilution hemofiltration [n = 36] and online pre-dilution HDF [n = 40]) was published by Locatelli et al. [49]. In comparison with low-flux HD, neither HF nor HDF significantly improved Hb levels or ESA requirements. The randomised CONvective TRAnsport STudy (CONTRAST) [50] compared low-flux HD with online HDF on survival in 714 participants. The effect of online HDF on

Table 12.2 Studies on the effect of HDF on anemia control and iron parameters

Author and year of publication	Design	N	HDF method, convection volume per session	Control group/ treatment at baseline	HDF effect on anemia/ESA	HDF effect on iron
Maduell 1999 [78]	Observational	37	Post-dilution, 24 L	Low-volume HDF, 4.1 L	Hb/Hct ↑; ESA ↓	Ferritin/TSAT=
Ward 2000 [46]	RCT	44	Post-dilution, 21 L	High-flux HD	Hb/Hct=; ESA=	NA
Wizeman 2000 [47]	RCT	44	Mid-dilution, 60 L (target)	Low-flux HD	Hct=; ESA=	NA
Bonforte 2002 [44]	Observational	32	Post-dilution 19.5 L	Low-flux HD	ESA +: Hb/ Hct=, ESA ↓; No ESA: Hb/ Hct ↑	Ferritin/TSAT=
Lin 2002 [43]	Cross-over	92	Post-dilution, 25.7 L	High-flux HD	Hct ↑; ESA ↓; ERI ↓	Ferritin/TSAT ↓
Vaslaki 2006 [45]	Randomized cross-over	129 (70 analyzed)	Post-dilution, 20.3 L (substitution)	Low-flux HD	ERI ↓	NA (iron policy changed during study)
Schiffl 2007 [59]	Randomized cross-over	76	Post-dilution, 19.1 L (substitution)	High-Flux HD (with starting phase on low-flux HD)	Hb/ESA = (but ESA ↓ compared to low-flux HD)	NA
Vilar 2009 [54]	Retrospective observational	858 (232 HDF)	Post-dilution 14.9 L (range 5.8–33.2)	High-flux HD	Hb ↑; ESA ↑; ERI =	NA
Pedrini 2011 [79]	Randomized cross-over	69	Pre-, mid- or postdilution; 48.5, 39.9, 22.0 L respectively	Low-flux HD	Hb=; ESA ↓; ERI =	NA

Oates 2011 [80]	Observational/semi-random	78 (34 HDF)	Post-dilution; 16.2–21.2 L (substitution)	High-flux HD	Hb=; ESA=	Iron dose ↑
Stefánsson 2012 [61]	Randomized cross-over	20	Post-dilution; 24.5 L	Low-flux HD	Hb=; ESA ↑	Ferritin ↓; hepcidin ↓
Ok 2013 (Turkish HDF study) [52]	RCT	782	Post-dilution; 17.2 L (substitution)	High-flux HD	Hb=; ESA ↓; ERI ↓	Ferritin/TSAT=
Maduell 2013 (ESHOL) [53]	RCT	906	Post-dilution; 22.9–23.9 L	High-flux HD	Hb=; ESA=	Ferritin/TSAT=; iron dose=
Van der Weerd 2014 (CONTRAST) [51]	RCT	714	Post-dilution; 20.7 L	Low-flux HD	Hb=; ESA=; ERI=	Ferritin=; TSAT ↓; iron dose=
Panichi 2014 [55]	Randomized cross-over (primary endpoint)	40	Post-dilution, 23.8 L	Low-flux HD	Hb=; ESA ↓; ERI ↓	Ferritin/TSAT=; iron dose =; hepcidin ↓

Hb/Hct hemoglobin/hematocrit, *ESA* erythropoiesis stimulating agents, *ERI* ESA resistance index (weight-adjusted ESA dose per hemoglobin unit), *TSAT* transferin saturation, *NA* not available

ESA resistance and iron parameters was a pre-specified secondary endpoint of this RCT [51]. After 12 months, ERI was not different between patients treated with HDF or HD. Even in the highest third of convection volume (>22 L), which was associated with a beneficial effect of HDF on mortality, there was no effect on ESA resistance. In these individuals only a trend towards a lower transferrin saturation ratio and lower ferritin levels was found, despite slightly more iron supplementation. The Turkish Online Haemodiafiltration Study [52] randomised 782 HD patients to either post-dilution online HDF (mean convection volume 19.6 L/session) or high-flux HD. Despite a similar clinical outcome in the two groups, the mean ESA dosage was significantly lower in the HDF group than in the HD patients (2282 ± 2121 versus 2852 ± 2702 U/week, respectively, P = 0.001). The On-Line Hemodiafiltration Survival Study (ESHOL) was a large, multicenter, open-label, RCT in which 906 chronic HD patients were randomised to continue standard HD (n = 450) or to switch to high-efficiency post-dilution online HDF (n = 456) [53]. Despite a significant reduction in all-cause and cardiovascular mortality, which were the primary endpoints, Hb levels and ESA dose did not differ between groups. Finally, it should be mentioned that increased ESA requirements in patients treated with HDF were reported as well in some studies [54, 61]. Apart from an inadequate study design, repeated blood loss due to recurring clotting in the extracorporeal circuit as a result of increased pro-coagulatory activity during HDF and increased post filter Ht levels in post-dilution HDF may play a role in this respect (see also Chap. 15).

Stimulated by the favourable results of ESHOL on clinical outcome, the REDERT study was designed to test the effect of high-volume (>20 L/session) HDF on ERI and hepcidin levels. In this two-arm, multicentre, crossover study, 40 stable HD patients were randomised to either online HDF or standard low-flux HD [55]. Interestingly, ERI was significantly reduced during the HDF period, while it increased during standard HD. Actually, Hb levels remained stable, while the total amount of ESAs administered during HD was considerably higher (HD 192,444 ± 131,341 versus HDF 135,955 ± 96,070 UI/6 months, respectively; p < 0.001). Hepcidin levels were also lower in HDF compared to standard HD.

Several factors could well explain the different results of the various trials. First, patient selection might play an important role, as stable patients without comorbidity or intercurrent illness, such as infections, may profit less from the beneficial effects of HDF on clinical outcome. Second, anaemia management is target driven and treating physicians may not necessarily adhere to the same guidelines because of cultural, geographical or economical reasons. Indeed, in multivariate analysis Locatelli et al. [49] found that the participating centre was the most significant predictor of Hb levels and ESA resistance, suggesting a large degree of heterogeneity among individual centres in treating anaemia. Third, the improved anaemia control in patients treated with HDF may not be caused by the effect of convective transport, but by the use of ultra pure dialysate. Many studies have shown that the use of ultrapure dialysis fluid results in increased Hb levels and diminished ESA requirements [56–58]. In this respect it should be mentioned that occasionally a beneficial effect of HDF on anaemia control was found when ultrapure dialysis fluid was not used in the control group (or at least dialysis fluid of inferior quality com-

pared to the fluid used for HDF) [52, 53, 56, 59]. Another factor that may contribute to the conflicting findings of HDF on anaemia control is the magnitude of the convection volume, which, as aforementioned, has been related to survival [60]. At present it is unclear whether there is also a dose-response effect on anaemia control. Finally, HDF may increase the clearance of erythropoiesis inhibiting toxins, although the concomitant removal of essential substances needed for erythropoiesis may occur as well. Examples of the first category are inflammatory toxins and hepcidin. Two studies showed a decrease in hepcidin levels in patients treated with HDF [55, 61], but only one of them showed improved ESA responsiveness [55]. In this respect, however, the treatment period of only 2 months may have been too short to obtain significant and reliable findings. Others showed an increased clearance of hepcidin with HDF as well [62], but also a substantial rebound of hepcidin levels already 1 h after a conventional HD session [63]. Since hepcidin is highly protein bound, its removal may differ according to dialysis the modality or membranes used [64]. Nevertheless, the reduced ferritin levels in patients treated with HDF in two studies may indicate an improved iron utilization, which may be mediated by reduced hepcidin levels because of a decrease in inflammation [44, 61]. No data are available on loss of substances, which are essential for erythropoiesis by HDF, except for vitamin C, which enhances iron availability [65].

Intensified Extracorporeal Dialysis Strategies

The clearance of MMW toxins by dialysis techniques is limited by their high intracorporeal mass transfer resistance [66]. As a result, optimal removal of these solutes by dialysis requires both enhanced convective clearance, such as with HDF, and increasing treatment time and/or frequency, which may diminish rebound from the extravascular space [67]. In this respect, increasing treatment frequency (short daily dialysis) or time (nocturnal dialysis or long dialysis), or both (daily nocturnal dialysis), may be interesting treatment options to improve ESA response, given their capacity of better removing MMW toxins [68]. The experience of the Tassin Centre in France showed good anaemia control in patients treated with low-flux HD three times per week for 8 h [69]. This effect is most likely mediated by the removal of small molecules, but also to a certain extent of MMW toxins, thanks to the very long dialysis time. Unfortunately, in this study no control group was included.

In 2008 a systematic review of small studies on the effects of short daily HD on various clinical parameters was published [70]. In six studies, the ESA dose was reduced, whereas in two studies no difference with standard HD was observed. The Frequent Hemodialysis Network (FHN) performed a trial on 245 patients who were randomized to either short daily or conventional HD [71]. The ESA dose was not different between both treatment arms, as were Hb levels [72]. Similarly, studies on the effect of increasing both treatment frequency *and* time, as in nocturnal HD, have shown mixed results [73, 74]. In a retrospective Canadian study, 63 patients treated with nocturnal HD had a rise in Hb levels and a fall in ESA requirements, whereas

iron saturation was lower compared to conventional dialysis [75]. In the FHN Nocturnal Trial, 87 patients were randomized to receive either nocturnal HD (six times/week for more than 6 h) or conventional HD [76]. In this study, ESA dose was not different between groups, despite lower doses of IV iron in those treated with nocturnal HD [72]. Finally, in a cross-over study 26 patients were switched from 4 to 5 h thrice-weekly HDF to 7–8 h nocturnal every-other-day HDF with the same (20–30 L) or higher (35–50 L) convective volume [77]. While nutritional status, phosphate and hypertension control improved and left ventricular mass (LVM) decreased over 12 months' of follow-up, in the higher convective volume group neither Hb levels, nor ESA index or iron parameters changed. In this respect it should be noted that more frequent and/or longer exposure to blood tubes, dialyzers and dialysis fluid, as well as repeated cannulations, may result in an enhanced inflammatory state and increased blood loss [67, 68], although in the FHN trial patients on nocturnal dialysis needed less iron supplementation than those treated with conventional HD [72].

Conclusion

Improving anaemia control in dialysis patients by removing erythropoiesis inhibiting toxins or substances involved in ESA responsiveness seems a logical and desired treatment option, since treatment with high ESA doses, especially in patients with a marked ERI, may be associated with detrimental effects. Over the past decades, many toxins that inhibit erythropoiesis and decrease red blood cell lifespan have been identified. Removal of these substances might have a beneficial effect on anaemia control. Treatment with HDF not only enhances the clearance of small and MMW uremic toxins, but also induces less inflammation than standard HD because of the ultrapure dialysis fluid applied. Therefore, HDF may, at least theoretically, have a beneficial effect on anaemia control and ESA resistance. However, results of clinical studies on this topic are conflicting and differ substantially with respect to the treatment protocol (including dialyzers and use of ultrapure dialysis fluid), control group and the treatment dose (i.e. applied convection volume). As for the effect of HDF on iron supplementation, data are even more limited. Considering alternative extracorporeal dialysis modalities, such as short daily HD or long/nocturnal HD, results of available studies are conflicting as well. Hence, when looking exclusively at anaemia control, no single treatment modality seems to be really preferable over the other.

Teaching Points

- Renal anemia is multifactorial and results from a decreased EPO production and responsiness, a shortened red blood cell survival (eryptosis) and/or shortage of essential nutritients
- ESA hypo-responsiness plays an important role in the risk of adverse effects

- Therefore, at present, the optimal Hb target concentration is unclear
- Uremic toxins contributing to ESA hypo-responsiness include toxic metabolites, inflammatory cytokines and gut derived protein-bound degradation products
- In ESKD patients the degree of anemia is correlated with Kt/V_{urea} up to 1.4. Higher dialysis doses do not improve anemia any further.
- Addition of a limited amount of convection (10–12 L/session), as occurs in high-flux HD, does not improve anemia control
- Conflicting reports have been published whether anemia control is improved by high volume HDF (convection volume >21 L/session)
- Available evidence suggest better iron utilization in high volume HDF

References

1. Pfeffer MA, Burdmann EA, Chen CY, et al.; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–32.
2. Del Vecchio L, Locatelli F. Safety issues related to erythropoiesis-stimulating agents used to treat anemia in patients with chronic kidney disease. Expert Opin Drug Saf. 2012;11(6): 923–31.
3. Zhang Y, Thamer M, Stefanik K, et al. Epoetin requirements predict mortality in hemodialysis patients. Am J Kidney Dis. 2004;44(5):866–76.
4. Panichi V, Rosati A, Bigazzi R, et al.; RISCAVID Study Group. Anaemia and resistance to erythropoiesis-stimulating agents as prognostic factors in haemodialysis patients: results from the RISCAVID study. Nephrol Dial Transplant. 2011;26(8):2641–8.
5. McCullough PA, Barnhart HX, Inrig JK, et al. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. Am J Nephrol. 2013;37(6):549–58.
6. Wagner M, Alam A, Zimmermann J, et al. Endogenous erythropoietin and the association with inflammation and mortality in diabetic chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(7):1573–9.
7. Kuroyanagi T, Saito M. Presence of toxic substances which inhibit erythropoiesis in serum of uremic nephrectomized rabbits. Tohoku J Exp Med. 1966;88(2):117–26.
8. Kushner D, Beckman B, Nguyen L, et al. Polyamines in the anemia of end-stage renal disease. Kidney Int. 1991;39(4):725–32.
9. Macdougall IC. Role of uremic toxins in exacerbating anemia in renal failure. Kidney Int Suppl. 2001;78:S67–72.
10. Galli F, Beninati S, Benedetti S, et al. Polymeric protein-polyamine conjugates: a new class of uremic toxins affecting erythropoiesis. Kidney Int Suppl. 2001;78:S73–6.
11. Jongen-Lavrencic M, Peeters HRM, Rozemuller H, et al. IL-6 induced anaemia in rats: possible pathogenetic implications for anaemia observed in chronic inflammations. Clin Exp Immunol. 1996;103:328–34.
12. Goicoechea M, Martin J, de Sequera P, et al. Role of cytokines in the response to erythropoietin in haemodialysis patients. Kidney Int. 1998;54:1337–43.
13. Panichi V, Migliori M, De Pietro S, Taccola D, et al. The link of biocompatibility to cytokine production. Kidney Int Suppl. 2000;76:S96–103.
14. Rattanasompattikul M, Molnar MZ, Zaritsky JJ, et al. Association of malnutrition-inflammation complex and responsiveness to erythropoiesis-stimulating agents in long-term hemodialysis patients. Nephrol Dial Transplant. 2013;28(7):1936–45.

15. De Lima GA, Mazzali M, Gentil AF, Plotegher L, Grotto HZ. Anemia in chronic renal disease: evaluation of inflammatory activity on erythropoiesis and iron metabolism in patients not submitted to dialysis treatment. Clin Lab. 2012;58(7–8):695–704.
16. Shooley JC, Kullgren B, Allison AC. Inhibition by interleukin-1 of the action of erythropoietin on erythroid precursors and its possible role in the pathogenesis of hypoplastic anaemias. Br J Haematol. 1987;67:11–7.
17. Cooper AC, Mikhail A, Lethbridge MW, Kemeny DM, Macdougall IC. Increased expression of erythropoiesis inhibiting cytokines (IFN-gamma, TNF-alpha, IL-10, and IL-13) by T cells in patients exhibiting a poor response to erythropoietin therapy. J Am Soc Nephrol. 2003;14(7):1776–84.
18. Kawashima Y, Sanaka T, Sugino N, Takahashi M, Mizoguchi H. Suppressive effect of quinolinic acid and hippuric acid on bone marrow erythroid growth and lymphocyte blast formation in uremia. Adv Exp Med Biol. 1987;223:69–72.
19. Pawlak D, Koda M, Pawlak S, Wolczynski S, Buczko W. Contribution of quinolinic acid in the development of anemia in renal insufficiency. Am J Physiol Renal Physiol. 2003;284(4): F693–700.
20. Tanaka T, Yamaguchi J, Higashijima Y, Nangaku M. Indoxyl sulfate signals for rapid mRNA stabilization of Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2) and suppresses the expression of hypoxia-inducible genes in experimental CKD and uremia. FASEB J. 2013;27(10):4059–75.
21. Lang E, Qadri SM, Lang F. Killing me softly – suicidal erythrocyte death. Int J Biochem Cell Biol. 2012;44(8):1236–43.
22. Ahmed M, Langer H, Abed M, Voelkl J, Lang F. The uremic toxin acrolein promotes suicidal erythrocyte death. Kidney Blood Press Res. 2013;37:158–67.
23. Ahmed MS, Abed M, Voelkl J, Lang F. Triggering of suicidal erythrocyte death by uremic toxin indoxyl sulfate. BMC Nephrol. 2013;14:244.
24. Radtke HW, Frei U, Erbes PM, Schoeppe W, Koch KM. Improving anemia by hemodialysis: effect of serum erythropoietin. Kidney Int. 1980;17(3):382–7.
25. Ifudu O, Feldman J, Friedman EA. The intensity of haemodialysis and the response to erythropoietin in patients with end-stage renal disease. N Engl J Med. 1996;334:420–5.
26. Madore F, Lowrie EG, Brugnara C, et al. Anemia in haemodialysis patients: variables affecting this outcome predictor. J Am Soc Nephrol. 1997;8:1921–9.
27. Coladonato JA, Frankenfield DL, Reddan DN, et al. Trends in anemia management among US haemodialysis patients. J Am Soc Nephrol. 2002;13:1288–95.
28. Movilli E, Cancarini GC, Zani R, Camerini C, Sandrini M, Maiorca R. Adequacy of dialysis reduces the doses of recombinant erythropoietin independently form the use of biocompatibles membranes in haemodialysis patients. Nephrol Dial Transplant. 2000;16:111–4.
29. Movilli E, Cancarini GC, Vizzardi V, et al. Epoetin requirement does not depend on dialysis dose when Kt/N > 1.33 in patients on regular dialysis treatment with cellulosic membranes and adequate iron stores. J Nephrol. 2003;16(4):546–51.
30. Gaweda AE, Goldsmith LJ, Brier ME, Aronoff GR. Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response. Clin J Am Soc Nephrol. 2010;5(4):576–81.
31. Kobayashi H, Ono T, Yamamoto N, et al. Removal of high molecular weight substances with large pore size membrane (BK-F). Kidney Dial. 1993;34(Suppl):154–7.
32. Villaverde M, Pérez-Garcia R, Verde E, et al. La polisulfona de alta permeabilidad mejora la respuesta de la anemia a la eritropoyetina en hemodialisis. Nefrologia. 1999;19:161–7.
33. Kawano Y, Takaue Y, Kuroda Y, Minkuchi J, Kawashima S. Effect on alleviation of renal anemia by haemodialysis using the high-flux dialyzer (BK-F). Kidney Dial. 1994;200–3.
34. Li Y, Wang Y, Lv J, Wang M. Clinical outcomes for maintenance hemodialysis patients using a high-flux (FX60) dialyzer. Ren Fail. 2013;35(9):1240–5.
35. Ayli D, Ayli M, Azak A, et al. The effect of high-flux hemodialysis on renal anemia. J Nephrol. 2004;17(5):701–6.
36. Locatelli F, Mastrangelo F, Redaelli B, et al. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. Kidney Int. 1996;50:1293–302.

37. Locatelli F, Del Vecchio L, Andrulli S. Dialysis: its role in optimizing recombinant erythropoietin treatment. Nephrol Dial Transplant. 2001;16 Suppl 7:29–35.
38. Yokoyama H, Kawaguchi T, Wada T, et al.; J-DOPPS Research Group. Biocompatibility and permeability of dialyzer membranes do not affect anemia, erythropoietin dosage or mortality in Japanese patients on chronic non-reuse hemodialysis: a prospective cohort study from the J-DOPPS II study. Nephron Clin Pract. 2008;109(2):c100–8.
39. Schneider A, Drechsler C, Krane V, et al.; MINOXIS Study Investigators. The effect of high-flux hemodialysis on hemoglobin concentrations in patients with CKD: results of the MINOXIS study. Clin J Am Soc Nephrol. 2012;7(1):52–9.
40. Locatelli F, Andrulli S, Pecchini F, et al. Effect of high-flux dialysis on the anaemia of haemodialysis patients. Nephrol Dial Transplant. 2000;15(9):1399–409.
41. Eknoyan G, Beck GJ, Cheung AK, et al. Hemo- dialysis (HEMO) study group: effect of dialysis dose and membrane flux on mortality and morbidity in maintenance hemodialysis patients: primary results of the HEMO study. N Engl J Med. 2002;347:2010–9.
42. Locatelli F, Martin-Malo A, Hannedouche T, et al.; Membrane Permeability Outcome (MPO) Study Group. Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol. 2009;20(3):645–54.
43. Lin CL, Huang CC, Yu CC, et al. Improved iron utilization and reduced erythropoietin resistance by on-line hemodiafiltration. Blood Purif. 2002;20(4):349–56.
44. Bonforte G, Grillo P, Zerbi S, Surian M. Improvement of anemia in haemodialysis patients treated by hemodiafiltration with high-volume on-line-prepared substitution fluid. Blood Purif. 2002;20:357–63.
45. Vaslaki L, Major L, Berta K, et al. On-line haemodiafiltration versus haemodialysis: stable haematocrit with less erythropoietin and improvement of other relevant blood parameters. Blood Purif. 2006;24(2):163–73.
46. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high flux haemodialysis: a prospective clinical study. J Am Soc Nephrol. 2000;11:2344–50.
47. Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomised study. Nephrol Dial Transplant. 2000;15 Suppl 1: 43–8.
48. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2013;28:2859–74.
49. Locatelli F, Altieri P, Andrulli S, et al. Predictors of haemoglobin levels and resistance to erythropoiesis-stimulating agents in patients treated with low-flux haemodialysis, haemofiltration and haemodiafiltration: results of a multicentre randomized and controlled trial. Nephrol Dial Transplant. 2012;27(9):3594–600.
50. Grooteman MPC, van den Dorpel MA, Bots ML, et al.; CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
51. van der Weerd NC, Den Hoedt CH, Blankestijn PJ, et al.; CONTRAST Investigators. Resistance to erythropoiesis stimulating agents in patients treated with online hemodiafiltration and ultrapure low-flux hemodialysis: results from a randomized controlled trial (CONTRAST). PLoS One. 2014;9(4):e94434.
52. Ok E, Asci G, Toz H, et al. On behalf of the 'Turkish Online Haemodiafiltration Study': mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF study. Nephrol Dial Transplant. 2013;28: 192–202.
53. Maduell F, Moreso F, Pons M, et al.; ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
54. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009;4:1944–53.

55. Panichi V, Scatena A, Rosati A, et al. High-volume online haemodiafiltration improves erythropoiesis-stimulating agents (ESA) resistance in comparison with low-flux bicarbonate dialysis: results of the REDERT study. Nephrol Dial Transplant. 2015;30(4):682–9.
56. Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. Nephrol Dial Transplant. 2013;28:438–46.
57. Sitter T, Bergner A, Schiffl H. Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. Nephrol Dial Transplant. 2000;15(8):1207–11.
58. Molina M, Navarro MJ, Palacios ME, et al. Importance of ultrapure dialysis liquid in response to the treatment of renal anaemia with darbepoetin in patients receiving haemodialysis. Nefrologia. 2007;27(2):196–201.
59. Schiffl H. Prospective randomized cross-over long-term comparison of online haemodiafiltration and ultrapure high-flux haemodialysis. Eur J Med Res. 2007;12:26–33.
60. Mostovaya IM, Blankestijn PJ, Bots ML, et al.; EUDIAL1 – an official ERA-EDTA Working Group. Clinical evidence on hemodiafiltration: a systematic review and a meta-analysis. Semin Dial. 2014;27(2):119–27.
61. Stefansson BV, Abramson M, Nilsson U, Haraldsson B. Hemodiafiltration improves plasma 25-hepcidin levels: a prospective, randomized, blinded, cross-over study comparing hemodialysis and hemodiafiltration. Nephron Extra. 2012;2:55–65.
62. Malyszko J, Malyszko JS, Kozminski P, Mysliwiec M. Type of renal replacement therapy and residual renal function may affect prohepcidin and hepcidin. Ren Fail. 2009;31:876–83.
63. Kuragano T, Shimonaka Y, Kida A, et al. Determinants of hepcidin in patients on maintenance hemodialysis: role of inflammation. Am J Nephrol. 2010;31:534–40.
64. Kuragano T, Furuta M, Shimonaka Y, et al. The removal of serum hepcidin by different dialysis membranes. Int J Artif Organs. 2013;36(9):633–9.
65. Morena M, Cristol JP, Bosc JY, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. Nephrol Dial Transplant. 2002;17:422–7.
66. Leypoldt JK, Cheung AK, Deeter RB, et al. Kinetics of urea and beta-microglobulin during and after short hemodialysis treatments. Kidney Int. 2004;66:1669–76.
67. Leypoldt JK. Kinetics of beta2-microglobulin and phosphate during hemodialysis: effects of treatment frequency and duration. Semin Dial. 2005;18:401–8.
68. Diaz-Buxo JA, White SA, Himmele R. Frequent hemodialysis: a critical review. Semin Dial. 2013;26:578–89.
69. Charra B, Chazot C, Jean G, et al. Long 3 x 8 hr dialysis: a three-decade summary. J Nephrol. 2003;16 Suppl 7:S64–9.
70. Punal J, Lema LV, Sanhez-Guisande D, Ruano-Ravina A. Clinical effectiveness and quality of life of conventional haemodialysis versus short daily haemodialysis: a systematic review. Nephrol Dial Transplant. 2008;23:2634–46.
71. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363:2287–300.
72. Ornt DB, Larive B, Rastogi A, et al. Impact of frequent hemodialysis on anemia management: results from the Frequent Hemodialysis Network (FHN) trials. Nephrol Dial Transplant. 2013;28:1888–98.
73. Walsh M, Culleton B, Tonelli M, Manns B. A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life. Kidney Int. 2005;67:1500–8.
74. Rao M, Muirhead N, Klarenbach S, Moist L, Lindsay RM. Management of anemia with quotidian hemodialysis. Am J Kidney Dis. 2003;42:18–23.
75. Schwartz DI, Pierratos A, Richardson RM, Fenton SS, Chan CT. Impact of nocturnal home hemodialysis on anemia management in patients with end-stage renal disease. Clin Nephrol. 2005;63:202–8.
76. Rocco MV, Lockridge Jr RS, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the frequent hemodialysis network nocturnal trial. Kidney Int. 2011;80:1080–91.

77. Maduell F, Arias M, Duran CE, et al. Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative. Nephrol Dial Transplant. 2012;27:1619–31.
78. Maduell F, del Pozo C, Garcia H, et al. Change from conventional haemodiafiltration to on-line haemodiafiltration. Nephrol Dial Transplant. 1999;14:1202–7.
79. Pedrini LA, De Cristofaro V, Comelli M, et al. Long-term effects of high-efficiency on-line haemodiafiltration on uraemic toxicity. A multicentre prospective randomized study. Nephrol Dial Transplant. 2011;26:2617–24.
80. Oates T, Pinney JH, Davenport A. Haemodiafiltration versus high-flux haemodialysis: effects on phosphate control and erythropoietin response. Am J Nephrol. 2011;33:70–5.

Chapter 13
Effects of Hemodiafiltration of Inflammation and Oxidative Stress

Andrew Davenport

Abstract Both observational and randomised trials comparing hemodiafiltration (HDF) with hemodialysis (HD) generally showed an improvement of the inflammatory state and oxidative stress in patients treated by HDF. Results do vary from study to study, however, not only due to differences in design and patient recruitment, but also secondary to differences in dialysis water quality, HDF mode and magnitude of the convection volume achieved. If HDF leads to a reduced (micro) inflammation in patients with chronic kidney disease, then the question arises as to whether this translates into clinically relevant measures. With respect to erythropoeitine (EPO) use, especially the earlier trials, when higher haemoglobin targets and greater use of erythropoietins were required, did suggest that HDF was associated with lower EPO requirements. These findings, however, were less clear in more recent large RCTs comparing online postdilution HDF with HD. Two prospective trials reported improved nutritional status with HDF, with objective changes in body composition as demonstrated by bioimpedance and DEXA scanning. There have been few studies which investigated whether switching from HD to HDF improved patient quality of life, and the results have been somewhat contradictory. Whether the small reduction in inflammation underlies the beneficial effect of high volume HDF on all cause and cardiovascular mortality, which is extensively discussed in Chap. 16, is an interesting, but currently unproven, option.

Keywords Inflammation • Hemodiafiltration • Oxidative stress • Advanced glycosylation end products (AGEs) • Convection • Cytokines

Abbreviations

CKD	Chronic kidney disease
CRP	C-reactive protein
ECC	Extra- corporeal circuit

A. Davenport, MD
UCL Centre for Nephrology, Royal Free Hospital, Pond St., London NW3 2QG, UK
e-mail: andrewdavenport@nhs.net

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_13

HD Hemodialysis
HDF Hemodiafiltration
IDH Intra-dialytic hypotension

Introduction

Patients with chronic kidney disease stage 5 (CKD5) have increased systemic inflammation and oxidative stress irrespective of whether they are managed conservatively or treated by dialysis. Progressive loss of residual renal function leads to the accumulation of uraemic toxins (Table 13.1). Some of these toxins, such as p-cresol and indoxyl sulfate are formed as by-product of tyrosine and phenylalanine, and tryptophan metabolism respectively, by bacteria in the gastrointestinal tract, whereas other uraemic toxins, including carbamylated albumin and other proteins accumulate due to increased production and others such as advanced glycosylation end (AGEs) products, β2 microglobulin, plasma light chains and circulating cell free DNA simply accumulate due to reduced renal clearance. However, in

Table 13.1 List of azotaemic toxins which predominantly affect the vascular endothelium

Uraemic toxin	Metabolism	Excretion	Synthesis	Pathophysiology
Small water soluble				
Guanidines (ADMA)	L arginine	↓	↑	Endothelium
Uric acid	Purines	↓		Endothelium
Phosphate	Diet	↓		Endothelium
Homocysteine	Methylation	↓	↑	Endothelium
Middle molecules				
FGF-23	Hormone	↓	↑	Endothelium
Leptin	Hormone	↓		Endothelium
PTH	Hormone		↑	Endothelium
Calciprotein	Particles	↓	↑	Endothelium
AGEs	Glucose	↓	↑	Endothelium
AOPPs	Dityrosine	↓	↑	Monocyte activation
Cell-free DNA	DNA	↓		Toll 9 receptor
Protein bound toxins				
P-cresyl	Tyrosine and phenylalanine		↑	Endothelium
Indoxyl sulfate	Tryptophan		↑	Endothelium
Carbamylation	Albumin		↑	Endothelium
Carbamylation	Lipoproteins		↑	Endothelium

ADMA Asymmetric dimethylarginine, *FGF-23* Fibroblast growth factor-23, *AGEs* advanced glycosylation end products, *AOPPs* advanced oxidized protein products

addition to inflammation driven directly as a consequence of the retention products of uraemia and treatments, there are additional pro-inflammatory factors (Table 13.2).

Several of these uremic toxins, including p-cresol, indoxyl sulfate, homocysteine, AGEs and β2 microglobulin have been reported to be independent risk factors for cardiovascular disease in the CKD5d patient [1–3]. After cardiovascular causes, infectious diseases are the next most common cause of death for dialysis patients with increased mortality rates being greatest for sepsis, followed in descending order by peritonitis, influenza, tuberculosis and pneumonia [4]. Patients with CKD are more susceptible to some infections, as the azotaemic state alters innate immunity, with reports of reduced monocyte Toll like receptor (TLR) 4 expression [5], reduced B lymphocyte cell populations [6], and impaired polymorphonuclear chemotaxis and phagocytosis [7] (Table 13.3). It has also been proposed that changes in the gastro-intestinal microbiota, due to the azotaemic milieu and changes in diet accompanied by increased intestinal permeability to endotoxin, results in a persistent activation of the innate immune system, with induction of regulatory mediators of the immune system which then suppress both innate and adaptive immunity [8]. Additionally, immune responses may also be impaired by poor nutritional status, malnutrition and vitamin D deficiency [9].

Inflammation leads to protein energy wasting (PEW), combining central appetite suppression, increasing risk of depression, insulin resistance with increased muscle breakdown and reduced physical activity. Inflammation leads to an increased endo-

Table 13.2 Patients with chronic kidney disease are at increased risk of both acute and chronic infections

	Infection	Risk factor
Chronic infections	Periodontal disease	Jaw bone loss
	Tuberculosis (TB)	Reactivation dormant TB
	C.pneumoniae	Reduced clearance
	H. pylori	Increased gastric urea
Acute infections	Urosepsis	Polycystic kidney disease
		Urogentinal abnormalities
	Septicaemia	S.Aureus colonisation
		Central venous catheters
		Arterio-venous (A-V) grafts
		Buttonhole A-V fistulae
	Lower respiratory tract infection	Pulmonary congestion
	Colitis	C.Difficile
Addition al risk	Co-morbidity	Diabetes mellitus
		Congestive cardiac failure
		Multiple myeloma
		Failed renal transplant
		Previous immunosuppression

Table 13.3 Changes in innate and adaptive immunity in patients with chronic kidney disease stage 5

Innate immunity	
Polymorphonuclear leukocytes	↑ numbers
	↑ basal activation
	↓ phagocytosis and bacterial killing
Macrophage/monocytes	↑ basal activation
NK cells	↓ numbers
Dendritic cells	↓ plasmacytoid dendritic cells
	↓ dendritic cell function
Adaptive immunity	
B cells	↓ B1 innate cells
	↓ convectional B2 cells
	↓ naïve B cells
	↓ memory B cells
T cells	↓ naïve T cells
	Phenotypically active
	↑ pro-apoptotic profile

thelial permeability and expansion of extracellular water, which in turn leads to macrophage recruitment and activation, increasing local inflammation and the production of reactive oxygen species, AGEs and advanced oxidised protein products (AOPPs) [10, 11]. This then leads to a vicious cycle which can be difficult to break in clinical practice.

Removal of Uremic Toxins by Hemodiafiltration (HDF)

HDF provides additional convective clearance compared to standard hemodialysis (HD). Small water soluble compounds such as uric acid are effectively removed by diffusion, so HDF, especially in predilution mode is less effective for urate clearance than HD. However, larger molecules such as asymmetric dimethylarginine (ADMA), with a molecular weight of just over 200 D, is more effectively cleared by postdilution HDF than HD [12]. Similarly both phosphate and β2 microglobulin clearance are increased by postdilution HDF compared to highflux HD [13]. Small peptide hormones such as leptin and FGF23 have increased clearance with on-line HDF [14, 15]. Both HDF and high flux HD have been reported to reduce circulating AGEs during a single treatment session, however postdilution HDF removes some 50 % more, and only HDF has been shown to produce a reduction in serum AGEs levels over time [16]. Similarly postdilution HDF clears more mitochondrial and cell free DNA fragments, during a treatment session, than highflux HD [17].

Studies measuring protein bound solute clearance have not demonstrated an advantage for postdilutional HDF over other dialytic modalities in removing

p-cresyl or indoxyl sulfate [13, 18]. However, a recent report has suggested that predilution HDF infusing a combination of hypertonic sodium infusate, coupled with a hyponatremic dialysate increases protein bound solutes by altering protein binding, so increasing the free proportion and allowing greater clearances [19].

As such, HDF generally offers advantages over standard HD in terms of clearance of the small and middle sized water soluble azotaemic toxins. Although convective clearance would in theory be greater with predilution mode for middle sized molecules, high convective volumes also dilute the concentration gradient and reduce diffusional losses. However for most middle sized solutes, clearance is equal or greater with postdilutional mode, as the concentration entering the dialyzer is higher, and membrane adsorption is also increased. When used in conventional pre or postdilution mode, HDF does not offer any increased clearance of protein bound azotaemic toxins.

Does Hemodiafiltration Reduce the Inflammatory Effect of Hemodialysis

As blood passes out through the patient's vascular access into the extracorporeal circuit (ECC), across the dialyzer, through the venous air detector chamber and then returns through the access, leukocytes, monocytes and platelets are activated. As the dialyzer has the greatest surface area of the extracorporeal circuit, this is the main site of activation. Complement proteins are also activated by dialyzers, with different dialyzer membrane compositions activating complement by different pathways; with polysulphone dialyzers causing classic complement pathway activation or lectin pathway activation and cellulosic dialyzers causing alternative pathway activation. Cellular activation leads to transcription of several proinflammatory cytokines, including TNFα , IL1β, IL-6, and IL-8, as well as chemokine receptors CXCR4 CCR7 CX3CR1, and other inflammatory mediators such as TWEAK, TRAIL and pentraxin 3. Monocyte and leukocyte activation also leads to surface blebbing and release of microparticles which trigger thrombin generation and clotting, and activation of the kinin-bradykin system. As bradykinin generation is pH dependent, then on-line priming with bicarbonate solutions increases pH and reduces bradykinin generation compared to priming with 0.9 % saline with haemodialysis [20]. HDF using ultrapure fluids has been reported to induce less monocyte and leukocyte activation and cytokine release compared to HD [21, 22].

HDF has been reported to reduce the frequency of hypotensive episodes during dialysis sessions compared to HD. Intermittent hypotensive episodes can potentially result in hypoperfusion and visceral ischemia. Although most interest has centred on reduction in cardiac blood supply and cardiac "stunning" during dialysis, other organs including the gastro-intestinal tract also suffer from ischaemia. Ischaemia, per se induces inflammatory changes. However intestinal ischaemia also leads to alteration in gut permeability, and so allows the potential for the

passage of bacterial derived endotoxin into the portal circulation. As such, some of the reduction in inflammatory changes reported with on-line HDF, may be consequent on a reduction in the inflammatory response to dialysis, due to the combination of improved dialysis water quality, reduced production or increased clearance of cytokines and inflammatory mediators generated by the passage of blood through the extracorporeal circuit, and reduced gut ischemia and endotoxin translocation.

Dialysis Water Risk in Hemodiafiltration

As large volumes of dialysis water are infused directly into the patient during on-line HDF treatments, then water quality is of paramount importance, and should comply with both microbiological standards for endotoxin and bacterial contamination to ensure ultra-pure water grade (<0.1 colony forming bacterial/ml and <0.03 EU/ml) as well as chemical purity [23]. In part some of the reports of reduced inflammatory changes associated with HDF may simply reflect switching to ultra-pure dialysis water.

Bacterial may form biofilm in the pipes supplying water to a dialysis unit, or contaminate bicarbonate or electrolyte mixtures. Although the current endotoxin filters will remove endotoxin and large bacterial DNA fragments [24], smaller fragments may pass through. Small fragments of bacterial DNA, up to 20 base pairs can potentially cross the current highflux dialyzers from the dialysate into the plasma water [25]. Bacterial DNA differs from human DNA in terms of methylation, and as such bacterial DNA fragments are detected and directly activate Toll like receptor 9 and provoke an inflammatory reaction.

Effects of Hemodiafiltration on Inflammation and Oxidative Stress

As renal function declines, the clearance of inflammatory mediators declines, and as such HDF, by adding convective clearance, may be expected to reduce the inflammatory milieu and oxidative stress of chronic kidney disease. Hence reports of HDF reducing circulating levels of IL-6 and TNFα, associated with a reduction in circulating proinflammatory monocytes (CD14+CD16+ positive cells) and C creative protein [26, 27]. Similarly HDF has been reported to reduce markers of oxidative stress, such as p22phox (the subunit of NAD(P)H oxidase), PAI-1, and oxidised plasma low density lipoproteins [28]. Others have demonstrated a reduction in reactive oxygen metabolites, and an increase in total anti-oxidant activity in both whole blood and lymphocytes [29, 30] and also increased heme-oxygenase-1, a protein involved in protection against the effects of oxidative damage and inflammation compared to patients treated by standard HD [31]. However longer term studies

showed that changes in anti-oxidant activity were more modest, than those reported in short term studies, with if anything a reduction in the antioxidant capacity of lymphocytes, with reduced concentrations of superoxide dismutase [32].

Inflammation is linked to endothelial dysfunction, with release of endothelial microparticles. Reports have suggested that CKD patients treated by HDF have lower circulating endothelial microparticles [33]. Although inducible monocyte nitric oxide synthase activity was shown not to be altered by HDF [31], the response to endothelial nitric oxide appears to be improved with increased brachial artery flow-mediated vasodilatation and carotid artery distensibility with HDF [34].

Clinical Effects of Hemodiafiltration

If HDF leads to a reduction in microinflammation in CKD patients, then the question arises as to whether this translates into clinically relevant measures. Comparative studies using ultrapure dialysate water comparing haemodialysis with hemodiafiltration have shown a variable effect on serum albumin, with some studies reporting an increase with HDF [35], and more recent reports not showing any differences in serum albumin over time [36, 37]. This may be due to the potentially greater losses of albumin with higher convection volume exchanges used in the more recent studies [36, 37]. Earlier studies also reported an improvement in nutritional status with HDF, as assessed by body mass index and fat mass [35]. However more importantly two studies observed that treatment with HDF led to an increase in lean body mass, measured by bioimpedance and DEXA techniques [35, 38].

Although earlier studies reported that treatment with HDF increased the response to erythropoietins, and reduced erythropoietin resistance [39, 40], this was not supported by more recent studies [41]. However both the targets for haemoglobin, and biologically available iron, have changed over time and as such lower doses of erythropoiesis stimulating agents are now used in clinical practice, which may well explain why the initial reports showed a positive effect for HDF when much higher doses were used compared to the current day. See also Chap. 12.

Inflammation has been linked to a greater prevalence of low mood and depression. Studies which have investigated whether HDF improves quality of life have produced varied results, with one study reporting that quality of life scores improved with HDF [38], whereas another failed to show any significant benefit [42] (Table 13.4).

Summary

Observational and randomised trials of HDF generally have reported that the introduction of HDF generally decreases the inflammatory milieu and increased oxidative stress of CKD. Results do vary from study to study, not only due to differences

Table 13.4 Reported benefits of hemodiafiltration treatment on inflammation compared to haemodialysis

Inflammatory mediators	Reportedly removed or reduced by hemodiafiltration
Cytokines	IL-1β [28]
	IL-6 [27, 29]
	IL-18 [43]
	TNF α [26, 43]
Oxidative stress	Superoxide dismutase [29, 32]
	Reactive oxygen metabolites [29]
	Oxidised low density lipoproteins [28]
Middle sized uraemic toxins	β2 microglobulin [14, 38, 44]
	Phosphate [39, 45]
	Advanced glycosylation end products [16]
	Advanced oxidized protein products [39]
	Pentosidin [39]
Cellular changes	Asymmetric dimethylarginine [12]
	activated monocytes (CD14+16+) [26, 46]
	Endothelial microparticles [46]
	Endothelial progenitor cells [46]

References in brackets

in patient recruitment, but also secondary to differences in dialysis water quality and HDF mode – predilution, mid-dilution and postdilution and mixed pre and postdilution, but more importantly the convective volume exchanged. In terms of translating these improvements in reducing microinflammation, then the earlier trials when higher haemoglobin targets and greater use of erythropoietins were required did suggest that HDF was associated with lower erthyropoietin requirements. In addition two prospective trials reported improved nutritional status with HDF with objective changes in body composition as demonstrated by bioimpedance and DEXA scanning. There have been few studies which investigated whether switching from HD to HDF improved patient quality of life, and the results have been somewhat contradictory [38, 42]. However the trials differed in terms of the mode of HDF and convective volumes delivered to be able to compare studies.

More recently randomised controlled trials have reported an overall survival benefit for HDF. Several studies have shown that the survival benefit was dependent upon the amount of convective clearance delivered [47, 48]. In addition as the survival benefit was predominantly for cardiovascular disease, then HDF by reducing microinflammation could potentially reduce vascular disease by modifying atheroma.

Teaching Points

- CKD patients not yet on dialysis already show signs of (micro)inflammation and oxidative stress
- Its causes are multifactorial, and result from reduced renal clearance, abnormal metabolic pathways and increased intestinal permeability for bacterial endotoxins

- During HD, the (micro)inflammatory state is aggravated by cellular and humoral activation within the ECC
- HDF may reduce (micro)inflammation by a reduction in IDH, and consequently, less intestinal hypoperfusion and a lower passage of bacterial endotoxins into the portal circulation
- In addition, several cytokines and other inflammatory mediators in the MMW range are better removed by HDF than by (highflux) HD
- Despite these findings, large recent RCTs failed to show clear differences in serum CRP and albumin levels between HD and HDF patients

References

1. Liabeuf S, Lenglet A, Desjardins L, Neirynck N, Glorieux G, Lemke HD, et al. Plasma beta-2 microglobulin is associated with cardiovascular disease in uremic patients. Kidney Int. 2012;82(12):1297–303.
2. Liabeuf S, Drueke TB, Massy ZA. Protein-bound uremic toxins: new insight from clinical studies. Toxins (Basel). 2011;3(7):911–9.
3. Furuya R, Kumagai H, Miyata T, Fukasawa H, Isobe S, Kinoshita N, et al. High plasma pentosidine level is accompanied with cardiovascular events in hemodialysis patients. Clin Exp Nephrol. 2012;16(3):421–6.
4. Wakasugi M, Kawamura K, Yamamoto S, Kazama JJ, Narita I. High mortality rate of infectious diseases in dialysis patients: a comparison with the general population in Japan. Ther Apher Dial. 2012;16(3):226–31.
5. Koc M, Toprak A, Arikan H, Odabasi Z, Elbir Y, Tulunay A, et al. Toll-like receptor expression in monocytes in patients with chronic kidney disease and haemodialysis: relation with inflammation. Nephrol Dial Transplant. 2011;26(3):955–63.
6. Pahl MV, Gollapudi S, Sepassi L, Gollapudi P, Elahimehr R, Vaziri ND. Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF receptor expression. Nephrol Dial Transplant. 2010;25(1):205–12.
7. Cohen G, Haag-Weber M, Horl WH. Immune dysfunction in uremia. Kidney Int Suppl. 1997;62:S79–82.
8. Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. Kidney Int. 2013;83(6):1010–6.
9. Stubbs JR, Idiculla A, Slusser J, Menard R, Quarles LD. Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. J Am Soc Nephrol. 2010;21(2):353–61.
10. Sukriti S, Tauseef M, Yazbeck P, Mehta D. Mechanisms regulating endothelial permeability. Pulm Circ. 2014;4(4):535–51.
11. Steyers III CM, Miller Jr FJ. Endothelial dysfunction in chronic inflammatory diseases. Int J Mol Sci. 2014;15(7):11324–49.
12. Zhang DL, Liu J, Liu S, Zhang Y, Liu WH. The differences of asymmetric dimethylarginine removal by different dialysis treatments. Ren Fail. 2010;32(8):935–40.
13. Meert N, Eloot S, Waterloos MA, Van LM, Dhondt A, Glorieux G, et al. Effective removal of protein-bound uraemic solutes by different convective strategies: a prospective trial. Nephrol Dial Transplant. 2009;24(2):562–70.
14. Mandolfo S, Borlandelli S, Imbasciati E. Leptin and beta2-microglobulin kinetics with three different dialysis modalities. Int J Artif Organs. 2006;29(10):949–55.
15. Patrier L, Dupuy AM, Granger VA, Chalabi L, Morena M, Canaud B, et al. FGF-23 removal is improved by on-line high-efficiency hemodiafiltration compared to conventional high flux hemodialysis. J Nephrol. 2013;26(2):342–9.

16. Lin CL, Huang CC, Yu CC, Yang HY, Chuang FR, Yang CW. Reduction of advanced glycation end product levels by on-line hemodiafiltration in long-term hemodialysis patients. Am J Kidney Dis. 2003;42(3):524–31.
17. Cao H, Ye H, Sun Z, Shen X, Song Z, Wu X, et al. Circulatory mitochondrial DNA is a pro-inflammatory agent in maintenance hemodialysis patients. PLoS One. 2014;9(12):e113179.
18. Krieter DH, Hackl A, Rodriguez A, Chenine L, Moragues HL, Lemke HD, et al. Protein-bound uraemic toxin removal in haemodialysis and post-dilution haemodiafiltration. Nephrol Dial Transplant. 2010;25(1):212–8.
19. Bohringer F, Jankowski V, Gajjala PR, Zidek W, Jankowski J. Release of uremic retention solutes from protein binding by hypertonic predilution hemodiafiltration. ASAIO J. 2015;61(1):55–60.
20. Coppo R, Amore A, Cirina P, Scelfo B, Giacchino F, Comune L, et al. Bradykinin and nitric oxide generation by dialysis membranes can be blunted by alkaline rinsing solutions. Kidney Int. 2000;58(2):881–8.
21. Todeschini M, Macconi D, Fernandez NG, Ghilardi M, Anabaya A, Binda E, et al. Effect of acetate-free biofiltration and bicarbonate hemodialysis on neutrophil activation. Am J Kidney Dis. 2002;40(4):783–93.
22. Kawabata K, Nakai S, Miwa M, Sugiura T, Otsuka Y, Shinzato T, et al. Changes in Mac-1 and CD14 expression on monocytes and serum soluble CD14 level during push/pull hemodiafiltration. Nephron. 2002;90(3):273–81.
23. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28(3):542–50.
24. Handelman GJ, Megdal PA, Handelman SK. Bacterial DNA in water and dialysate: detection and significance for patient outcomes. Blood Purif. 2009;27(1):81–5.
25. Tao X, Hoenich N, Handelman SK, Levin NW, Kotanko P, Handelman GJ. Transfer of low-molecular weight single-stranded DNA through the membrane of a high-flux dialyzer. Int J Artif Organs. 2014;37(7):529–38.
26. Carracedo J, Merino A, Nogueras S, Carretero D, Berdud I, Ramirez R, et al. On-line hemodiafiltration reduces the proinflammatory CD14+CD16+ monocyte-derived dendritic cells: a prospective, crossover study. J Am Soc Nephrol. 2006;17(8):2315–21.
27. Panichi V, Manca-Rizza G, Paoletti S, Taccola D, Consani C, Filippi C, et al. Effects on inflammatory and nutritional markers of haemodiafiltration with online regeneration of ultrafiltrate (HFR) vs online haemodiafiltration: a cross-over randomized multicentre trial. Nephrol Dial Transplant. 2006;21(3):756–62.
28. Calo LA, Naso A, Carraro G, Wratten ML, Pagnin E, Bertipaglia L, et al. Effect of haemodiafiltration with online regeneration of ultrafiltrate on oxidative stress in dialysis patients. Nephrol Dial Transplant. 2007;22(5):1413–9.
29. Filiopoulos V, Hadjiyannakos D, Metaxaki P, Sideris V, Takouli L, Anogiati A, et al. Inflammation and oxidative stress in patients on hemodiafiltration. Am J Nephrol. 2008;28(6):949–57.
30. Gonzalez-Diez B, Cavia M, Torres G, Abaigar P, Muniz P. Effect of a hemodiafiltration session with on-line regeneration of the ultrafiltrate on oxidative stress. Comparative study with conventional hemodialysis with polysulfone. Blood Purif. 2008;26(6):505–10.
31. Calo LA, Naso A, Davis PA, Pagnin E, Corradini R, Tommasi A, et al. Hemodiafiltration with online regeneration of ultrafiltrate: effect on heme-oxygenase-1 and inducible subunit of nitric oxide synthase and implication for oxidative stress and inflammation. Artif Organs. 2011;35(2):183–7.
32. Gonzalez-Diez B, Cavia M, Torres G, Abaigar P, Camarero V, Muniz P. The effects of 1-year treatment with a haemodiafiltration with on-line regeneration of ultrafiltrate (HFR) dialysis on biomarkers of oxidative stress in patients with chronic renal failure. Mol Biol Rep. 2012;39(1):629–34.
33. Ariza F, Merino A, Carracedo J, Alvarez de Lara MA, Crespo R, Ramirez R, et al. Post-dilution high convective transport improves microinflammation and endothelial dysfunction independently of the technique. Blood Purif. 2013;35(4):270–8.

34. Bellien J, Freguin-Bouilland C, Joannides R, Hanoy M, Remy-Jouet I, Monteil C, et al. High-efficiency on-line haemodiafiltration improves conduit artery endothelial function compared with high-flux haemodialysis in end-stage renal disease patients. Nephrol Dial Transplant. 2014;29(2):414–22.
35. Savica V, Ciolino F, Monardo P, Mallamace A, Savica R, Santoro D, et al. Nutritional status in hemodialysis patients: options for on-line convective treatment. J Ren Nutr. 2006; 16(3):237–40.
36. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Penne EL, Mazairac AH, et al. Clinical predictors of decline in nutritional parameters over time in ESRD. Clin J Am Soc Nephrol. 2014;9(2):318–25.
37. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Mazairac AH, Penne EL, et al. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. Kidney Int. 2014;86(2):423–32.
38. Beerenhout CH, Luik AJ, Jeuken-Mertens SG, Bekers O, Menheere P, Hover L, et al. Predilution on-line haemofiltration vs low-flux haemodialysis: a randomized prospective study. Nephrol Dial Transplant. 2005;20(6):1155–63.
39. Vaslaki L, Major L, Berta K, Karatson A, Misz M, Pethoe F, et al. On-line haemodiafiltration versus haemodialysis: stable haematocrit with less erythropoietin and improvement of other relevant blood parameters. Blood Purif. 2006;24(2):163–73.
40. Bonforte G, Grillo P, Zerbi S, Surian M. Improvement of anemia in hemodialysis patients treated by hemodiafiltration with high-volume on-line-prepared substitution fluid. Blood Purif. 2002;20(4):357–63.
41. van der Weerd NC, den Hoedt CH, Blankestijn PJ, Bots ML, van den Dorpel MA, Levesque R, et al. Resistance to erythropoiesis stimulating agents in patients treated with online hemodiafiltration and ultrapure low-flux hemodialysis: results from a randomized controlled trial (CONTRAST). PLoS One. 2014;9(4):e94434.
42. Mazairac AH, de Wit GA, Grooteman MP, Penne EL, van der Weerd NC, den Hoedt CH, et al. Effect of hemodiafiltration on quality of life over time. Clin J Am Soc Nephrol. 2013;8(1): 82–9.
43. Kuo HL, Chou CY, Liu YL, Yang YF, Huang CC, Lin HH. Reduction of pro-inflammatory cytokines through hemodiafiltration. Ren Fail. 2008;30(8):796–800.
44. Oates T, Pinney JH, Davenport A. Haemodiafiltration versus high-flux haemodialysis: effects on phosphate control and erythropoietin response. Am J Nephrol. 2011;33(1):70–5.
45. Penne EL, van der Weerd NC, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55(1):77–87.
46. Ramirez R, Carracedo J, Merino A, Nogueras S, varez-Lara MA, Rodriguez M, et al. Microinflammation induces endothelial damage in hemodialysis patients: the role of convective transport. Kidney Int. 2007;72(1):108–13.
47. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.
48. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.

Chapter 14
Effects on the Removal of Uremic Toxins

Griet L.R.L. Glorieux and Detlef H. Krieter

Abstract From the moment kidney function declines, retention of many different uremic solutes starts. Many of these solutes exert pathophysiological effects playing a role in cardiovascular damage, a major cause of morbidity and mortality in chronic kidney disease. Over the past years, middle molecules (e.g. cytokines and advanced glycation end-products (AGEs)) but especially protein-bound solutes (e.g. indoxyl sulfate and p-cresyl sulfate) have been identified as some of the main toxins associated with vascular disease affecting the major cell types involved (endothelial cells, leukocytes, platelets and/or vascular smooth muscle cells). Many of these solutes, however, are difficult to remove by standard dialysis strategies. The removal of the larger middle molecules can be obtained by increasing dialyzer pore size and by applying hemodiafiltration (HDF). The removal of protein-bound solutes, however, remains limited with all current dialysis strategies, because only the free fraction of the solute is available for, mostly diffusive, removal. For the future, alternative measures, complementing dialysis removal, will have to be developed to more effectively decrease circulating levels of the difficult-to-remove uremic toxins.

Keywords Uremic toxins • Biological effects • Removal • Hemodialysis • Hemodiafiltration

G.L.R.L. Glorieux, MSc, PhD (✉)
Nephrology Division, Department of Internal Medicine, Ghent University Hospital, De Pintelaan 185, 0K12IA, Gent 9000, Belgium
e-mail: griet.glorieux@ugent.be

D.H. Krieter, PhD
Division of Nephrology, Department of Medicine I, University Hospital Würzburg, Würzburg, Germany

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_14

Introduction

From the moment kidney function declines, retention of many different uremic solutes starts. The kinetics of this process remain, however, far from clear. Over the years, the list of known uremic retention solutes has become progressively longer [1, 2], which can be attributed to improvements in analytic techniques and recent advances in the area of "-omics," allowing the detection of a myriad of previously unknown compounds [3, 4]. In addition, the presence of an indefinite number of posttranslational modifications of retention solutes, with each of the structural variants possibly exerting a pathophysiologic impact that differs from the mother compound, hampers the process of mapping the uremic retention solutes even more. For the time being, uremic solutes are preferentially classified according to the physicochemical characteristics affecting their clearance during dialysis which, as of today, is still the main therapeutic option for their removal. Traditionally, this subdivision focuses on three types of molecules: the small water-soluble compounds (molecular weight (MW <500 Da), the larger 'middle molecules' (MW >500 Da) and the protein-bound compounds [2]. Recent reviews point out that removal of small water-soluble compounds is important for 'acute mortality' (e.g. related to hyperkalemia, sodium removal), but that for the chronic problems of the uremic syndrome, the protein-bound solutes and the middle molecules seem to play a more essential role [5–7]. HDF combines the advantages of hemodialysis (HD), small solute removal by diffusion, with those of hemofiltration (HF), large solute removal by convection. Besides a wider molecular weight range of solutes removed, the combination of diffusive and convective transport provides more total clearance per unit of surface area than the application of each of both processes separately [8]. Nevertheless, the combination does not result in the simple summation of clearance delivered by each of the separate elements. To estimate the relative contributions of diffusion and filtration to the clearance, the equation below can be used [9]:

$$C_{total} = C_{diff} + \left[Q_{UF} / 2\right]\left(\text{mL} / \text{min}\right)$$

where C_{total} is the total clearance, C_{diff} the diffusive clearance and Q_{UF} the ultrafiltration rate. This equation is valid for postdilution HDF and ultrafiltration rates up to 100 mL/min.

Addition of convection reduces diffusive clearance. As diffusive clearance is most pronounced for small molecules, this reduction due to convection will proportionately be more important for these solutes, or more exactly, the gain in clearance due to convection will proportionately be more important for larger "middle" molecules [8].

This chapter will focus on those compounds with convincing biological effects associated to adverse outcome, see Table 14.1. Beneficial effects of their removal by HDF will be discussed.

Table 14.1 Overview on uremic toxins relevant for removal by HDF

Uremic retention solute	Normal concentration	Uremic concentration Mean (SD or range)	Ratio U/N Mean (SD or range)	Max. RR (%) in HDF
Small water-soluble				
Phosphate (mg/dL)	2.6–4.5	>5	2	<60[a]
Middle molecules				
β2-microglobulin (mg/L)	1.9 (1.6)	43.1 (18)	22.7	80
Interleukin-6 (ng/L)	4.0	8.6 (3.7)	2.1	NA
Tumor necrosis factor- α (ng/L)	7.0	57.8 (10.8)	8.2	NA
Fibroblast growth factor-23 (ng/L)	26.3 (0.8)	149.6 (102.8)	5.7	NA
Complement factor D (mg/L)	1.9 (0.5)	20.6 (13.0)	10.8	NA
Protein-bound				
p-cresyl sulfate (mg/L)	1.9 (1.3)	41 (13.3)	21.6	<50
Indoxyl sulfate (mg/L)	0.53 (0.29)	44.5 (15.3)	84.0	<50
Indole acetic acid (mg/L)	0.5 (0.3)	2.4 (2.2)	4.8	<50
Hippuric acid (mg/L)	3.0 (2.0)	87.2 (61.7)	29.1	75
Advanced glycation end-products				
N-carboxymethyl-lysine (mg/L)	0.35 (0.13)	18.5 (5.0)	5.3	NA
Pentosidine (μg/L)	51.6 (18.8)	579.5 (299.3)	11.2	

Based on data from Duranton et al. [1]
NA not available
[a]Reduction Ratio (RR) not appropriate because of phosphate refilling in case of falling below the individually different threshold level

Which Solutes Should Be Removed?

Small Water-Soluble Compounds

Phosphate (95 Da) is one of the smallest solutes qualified as uremic toxin [2, 10]. It accumulates in chronic kidney disease (CKD) and leads to adverse effects on biological systems. Hyperphosphatemia contributes to metabolic disturbances such as hyperparathyroidism, vitamin D resistance, and hypocalcemia. It leads to organ damage particularly of the parathyroid glands, bones, and most importantly the cardiovascular system. Elevated phosphorus levels are associated with arterial and valvular calcification, arteriosclerosis, and an increased risk of cardiovascular death [11, 12]. For further reading, see Chap. 11.

Middle Molecules

The group of middle molecules is mainly composed of small peptides. Many of these are implied in cardiovascular disease, by causing inflammation, endothelial damage, smooth muscle cell proliferation, activation of coagulation or by interfering with calcium/phosphorus household [13]. There is thus a pathophysiologic rationale for optimizing their removal. However, their effect on relevant cell mechanisms at the concentrations occurring in uremia has barely been studied. Data on the association of middle molecule concentrations with clinical outcome parameters are more elaborate.

β2-Microglobulin

The most widely-used surrogate marker for middle molecule retention and removal is β2-microglobulin (β2M; 11.8 kDa). It is the β-chain of the major histocompatibility complex and is expressed on most nucleated cells. Free β2M circulates in the blood as a result of shedding from cell surfaces or intracellular release. In general, this molecule is, however, considered inert. Nevertheless, Wilson et al. [14] identified by proteomic analysis β2-microglobulin as the most adequate marker of severity of peripheral vascular disease in a population with no or moderate CKD. In addition, β2-microglobulin has been associated with arterial stiffness in the general population [15] and bone remodeling in non-CKD postmenopausal women [16]. With regard to outcome studies, in two secondary analyses of the HEMO study conducted in HD patients, β2-microglobulin was related to overall and infectious mortality [17, 18]. Higher β2M levels correlate with various cardiovascular risk factors and inflammation markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [19], and are associated independently with cardiovascular mortality and cardiovascular events [20]. However, when the oxidative burst of leukocytes was investigated, β2M did not show proinflammatory properties and therefore may not by itself be a causative factor of vascular damage [21]. The serum β2M level is also a new predictor of diabetes-related mortality in diabetic patients irrespective of renal function [22] and is associated positively with insulin resistance [23].

Cytokines

The concentration of cytokines gradually increases in CKD [24], which is thought to be mainly attributed to an increased generation in response to uremic toxins [25–27] and reduced renal clearance [28, 29]. According to the former, cytokines can be considered as secondary uremic retention solutes. Among several pro-inflammatory cytokines, only TNFα revealed to exert pro-oxidative effects on leukocytes at high range uremic concentrations [30]. In a population at different stages of CKD, IL-6 (24.5 kDa) was related to mortality, whereas there was no association for TNF-α (26 kDa). The latter was confirmed in a selected CKD stage 4–5 group [30, 31].

In contrast, in a HD population, TNF-α was a stronger predictor of mortality than IL-6 [32].

In view of improving removal of cytokines, also anti-inflammatory cytokines like interleukin 10 (IL-10, 18 kDa) of which their generation is increased in response to low-grade inflammation in CKD, will be removed. IL-10 is capable of effective down-regulation of proinflammatory cytokines, chemotactic factors and adhesion molecules [33]. A possible beneficial role of IL-10 in CKD has been proposed by Girndt et al. [34], showing that genetic polymorphisms leading to low IL-10 concentration are associated with increased cardiovascular risk in dialysis patients. So, beneficial effects are to be expected only when an equilibrium between pro- and anti-inflammatory factors is restored.

Fibroblast Growth Factor-23

Elevated levels of fibroblast growth factor-23 (FGF-23, 32 kDa), a molecule essentially linked to bone mineral homeostasis, has been associated with progression of kidney failure [35], cardiac dysfunction [36] and overall mortality [37, 38]. Although merely seen as a marker, a recent study in animals showed a direct hypertrophic effect on the heart after chronic injection [39]. These data thus suggest that middle molecule removal could favor outcome, see also Chap. 11.

Complement Factor D

Complement factor D (24 kD) is involved in the regulation of the alternative complement pathway. Due to accumulation in the intravascular compartment [40], serum concentrations are increased in CKD [41]. Elevated complement factor D concentrations enhance the activity of the alternative complement pathway [42] and inhibit neutrophil degranulation [43].

Protein-Bound Compounds

The toxicity of retained protein-bound solutes, which are largely intestinally generated, remains a matter of debate, as in many experimental studies excessively high free concentrations resulted in an overestimation of their potential toxicity [44].

Indoxyl Sulfate and p-Cresyl Sulfate

A recent systematic review unraveled 27 studies where adequate free concentrations of two prototypic protein-bound solutes, p-cresyl sulfate (pCS; 188 Da) and indoxyl sulfate (IS; 212 Da), had been applied [45]. Interference was shown with several key

metabolic processes involved in the uremic syndrome, such as inflammation, oxidative stress, endothelial dysfunction, leukocyte-endothelial interaction, epithelial-to-mesenchymal transition, cardiac cell proliferation and renal tubular cell senescence. These data refer to cardio-vascular morbidity and mortality and to the progression of renal failure. Together with observational studies showing a highly significant association between concentrations of protein-bound toxins and hard endpoints, such as cardio-vascular events, progression of renal failure and mortality [46–51], these data offer strong arguments in favor of a key role of IS and pCS in the uremic syndrome. Since then, additional reports supporting the above evidence were published, covering: increased cross-talk between leukocytes and endothelium, glycocalyx degradation and vascular leakage [52]; apoptosis of osteoblasts [53]; inhibition of drug metabolism [54]; induction of tubular endothelial growth factor receptor leading to tissue remodeling [55]; and inhibition of breakdown of angiotensin II [56].

Indole Acetic Acid

Similar effects were also described for other protein-bound toxins [57]. Indole acetic acid (IAA; 175 Da) was shown to inhibit endothelial progenitor cell production opposing their beneficial effect on vessel repair and neovascularization [58]. IAA induces endothelial inflammation and oxidative stress and activates an inflammatory AhR/p38MAPK/NF-ƙB pathway [59]. Recently, the ability of IAA to induce tissue factor production that was associated with increased pro-coagulant activity was revealed [60, 61]. The induction of tissue factor occurred via the aryl hydrocarbon–receptor pathway [61] In addition, serum IAA is an independent predictor of mortality and cardiovascular events in patients with CKD [59].

Hippurates

Metabolome studies repeatedly pointed to accumulation of hippurates. Boelaert et al. demonstrated an increase, already from CKD stage 3 on, of the known hippuric acid, 2-,3-,4-hydroxyhippuric acid and the unknown aminohydroxyhippuric acid and sulfate and glucuronide conjugates of hydroxyhippuric acid [3]. Hippuric acid (HA; 179 Da) was first isolated from horse urine, hence its name, and is a microbial co-metabolite. It originates from polyphenolic compounds in the diet such as fruit vegetables, tea and coffee, metabolised to form benzoic acid which is at the site of the liver and renal cortex conjugated to glycine to form hippuric acid [62]. In general, literature on toxic effects of hippurate is fairly old; somewhere along the way, interest in HA got lost. Satoh et al. demonstrated that sub-totally nephrectomized rats given HA in their drinking water showed a decrease in inulin clearance, pointing to glomerular dysfunction. This was supported by the significant increase in whole kidney sclerosis index. In addition, NAG (N acetyl glucoseaminidase) excretion rate, an indicator of proximal tubular injury, was higher in the uremic toxin overloaded rats compared to the control rats [63]. More recently, HA was shown to inhibit the transport of two important efflux pumps

expressed on human tubular cells [64]. Next to hippurate, hydroxyhippurates were increased in plasma from CKD patients. p-Hydroxyhippuric acid (p-OHHA) inhibits Ca^{2+}-ATPases, needed for restoring intracellular Ca^{2+} homeostasis after cell activation. Increased $[Ca^{2+}]_i$ modulates various polymorphonuclear leukocyte functions such as oxidative burst and degranulation as well as apoptosis as demonstrated by Cohen by the decrease in caspase activity in PMNL in the presence of p-OHHA [65].

Advanced Glycation End Products

The link between the accumulation of AGEs and inflammation has been emphasized before [66]. Nutritional AGEs contribute to this effect since AGE-rich food administered to diabetics increased endothelial free radical production and decreased arterial responsiveness to vasodilatory stimuli [67]. The main representatives of the AGE group are N-carboxymethyl-lysine, pentosidine, and methylglyoxal. Plasma pentosidine is associated with inflammation and malnutrition in ESRD patients starting dialysis therapy [68]. The receptor for AGEs has been shown to exert direct effects on nuclear factor-κB activation in dialysis patients [69], in its turn leading to activation of the inflammatory cascade. The receptor for AGE ligand S100A12 (also known as EN-RAGE) contributes to inflammation and the development of atherosclerosis, and has shown an association with mortality risk in HD patients [70]. As markers of oxidative stress, AGEs also contribute to the activity of inflammatory processes, and are believed to participate in atherosclerosis progression, mainly through modification of matrix proteins, platelet aggregation, defective vascular relaxation, and abnormal lipoprotein metabolism [71].

Influence of HDF on Uremic Toxin Removal

Removal of Small Solutes

By adding of a diffusive component, low small solute removal, the major drawback of purely convective HF, has been overcome in HDF. Depending on the flow settings, small solute clearance in online postdilution HDF is even superior compared to low- and high-flux HD, although this effect is rather modest [72–75]. However, the site of the infusion is crucial because in predilution HDF, small solute clearance is not improved and can be even worsened [76, 77].

The removal of phosphate by dialysis differs from a typical small solute such as urea; it rather resembles that of a middle molecule. This is explained by the electric charge of the phosphate molecule, resulting in the attachment of surrounding water molecules and, consequently, a behaviour like a larger solute. Due to its complex transport kinetics deriving from a four compartmental distribution in the body, the elimination of phosphate during 4–5 h lasting dialysis sessions is limited [78]. Also a consequence of the complex kinetics, the determination of reduction ratios must be regarded as an inade-

quate measure for phosphate removal. Despite continued elimination of phosphate, refilling from the third and fourth compartment to maintaining an individually different minimum serum phosphate level prevents results exceeding 60 % [78].

Nevertheless, a number of studies have proven a superior clearance of phosphate during postdilution HDF compared to standard HD [79–81]. Improvements of the instantaneous plasma clearance between 10 % and 15 % have been determined [73]. This beneficial effect from single sessions may also result in a better control of the phosphate level over longer terms [80]. The large Dutch CONTRAST study demonstrated a decrease of the phosphate level from 5.18 to 4.87 mg/dL and an increase of the proportion of patients reaching phosphate treatment targets from 64 to 74 % over a 6-month period in patients randomized to postdilution HDF. No such changes were observed in patients on low-flux HD [82]. Similar results over 12 months were obtained by a smaller British study comparing postdilution HDF to high-flux HD [83], but several other trials failed to show an advantage of online HDF [84, 85], underlining the need for a control of the dietary phosphorus intake, use of oral phosphate binders, and residual renal function in investigations on phosphorous homeostasis [86].

Removal of Middle Molecules

Convection is the driving force for the removal of large solutes, which pass the dialysis membrane almost exclusively by solute drag effectuated by the transmembrane ultrafiltration of plasma water [87]. Clinical studies investigating the treatment efficacy of convective therapy procedures mostly measured the elimination of β2M as the surrogate parameter for middle molecule removal, not least due to historical reasons: Years before an association of the predialysis β2M level with mortality became evident [17, 20], β2M was shown to play a major role in dialysis-associated amyloidosis, which may be retarded by efficient β2M removal [88].

As indicated above, β2M elimination during a single session correlates with convective volume [89, 90]. Numerous studies have demonstrated a considerably increased β2M removal in online HDF versus HD [74, 91, 92]. At optimum settings of the flow rates, a reduction of the pretreatment β2M level of up to 80 % during a 4 h HDF session is achievable. Compared to high-flux HD, a recent trial investigating last generation high-flux dialysis membranes found an improvement of instantaneous plasma clearance and reduction ratio, established efficacy parameters for β2M removal, in online postdilution HDF of 60 % and 15 %, respectively [73]. This considerable difference was even more pronounced for larger marker molecules, such as cystatin C (13.3 Da) and myoglobin (17.6 kDA), although, treatment settings in HD and high-efficiency HDF were kept identical, except for the substitution flow rate [73].

A beneficial effect of improved single session β2M removal on pretreatment β2M levels over the long-term has been shown, when online HDF was compared to

low-flux HD, a dialysis form not eliminating middle molecules [92]. This effect was particularly obvious in patients without residual renal function [93]. Compared to high-flux HD, lower predialysis β2M levels over longer periods of time after a switch to online HDF were not consistently observed. Some observational studies were able to show such a difference [83, 89], while other randomized trials did not [75, 85]. Again, this finding underlines the importance of the residual renal function for predialysis β2M because differences in the levels between high-flux HD and HDF can be found in patients without any urine production [94].

The removal of other potentially relevant large solutes had been examined in only very few, mostly single center studies. Thus, their results must be interpreted with some caution. Together with lower pretreatment concentrations over a 12 month period, a significant better elimination of complement factor D in postdilution HDF compared to high-flux HD was demonstrated by Ward et al. [75]. Serum levels of TNF-α, a cytokine linked to the inflammatory response, were shown to increase during low-flux HD, while they decreased during high-flux HD and even more during online HDF [95]. This effect may well result from more intense elimination, but biocompatibility effects triggering the inflammatory response to the different dialysis procedures cannot be completely ruled out. However, a small scale study randomizing septic patients with acute renal failure to either high-flux HD or online HDF demonstrated higher reduction ratios of several plasma cytokine levels, including vascular endothelial growth factor, interleukin 6, 8, and 10 as well as TNF-α in HDF [96].

Compared to high-flux HD, online HDF also better removes the relatively large molecule FGF-23, achieving reduction ratios of 56 % versus 36 % [97]. This potentially favorable effect is particularly pronounced when the treatment length is extended to 8 h [79].

Removal of Protein-Bound Solutes

Protein-bound toxins are difficult to remove by extracorporeal renal replacement therapies. The protein-bound fraction is retained and only the free, mostly low-molecular solute can pass the dialysis membrane without differences between low- and high-flux HD [98]. The high ratio of distribution volume to clearance further affects the elimination of these substances [99], allowing only inadequate removal with current dialysis strategies. Compared with diffusive measures, i.e., higher dialysate flow rate and larger dialyzer surface area [100], the effect of convection on protein-bound solute removal is poor. Thus, increasing the ultrafiltration flow rate is little effective to improve the clearance [101]. Accordingly, clinical studies comparing the efficacy of protein-bound solute removal during online HDF with HD have shown only marginal or no differences. Most of these studies focused on the removal of the small compounds p-cresol or its main in vivo metabolite pCS, others additionally measured the also highly protein-bound IS as surrogate markers for protein-bound toxin removal.

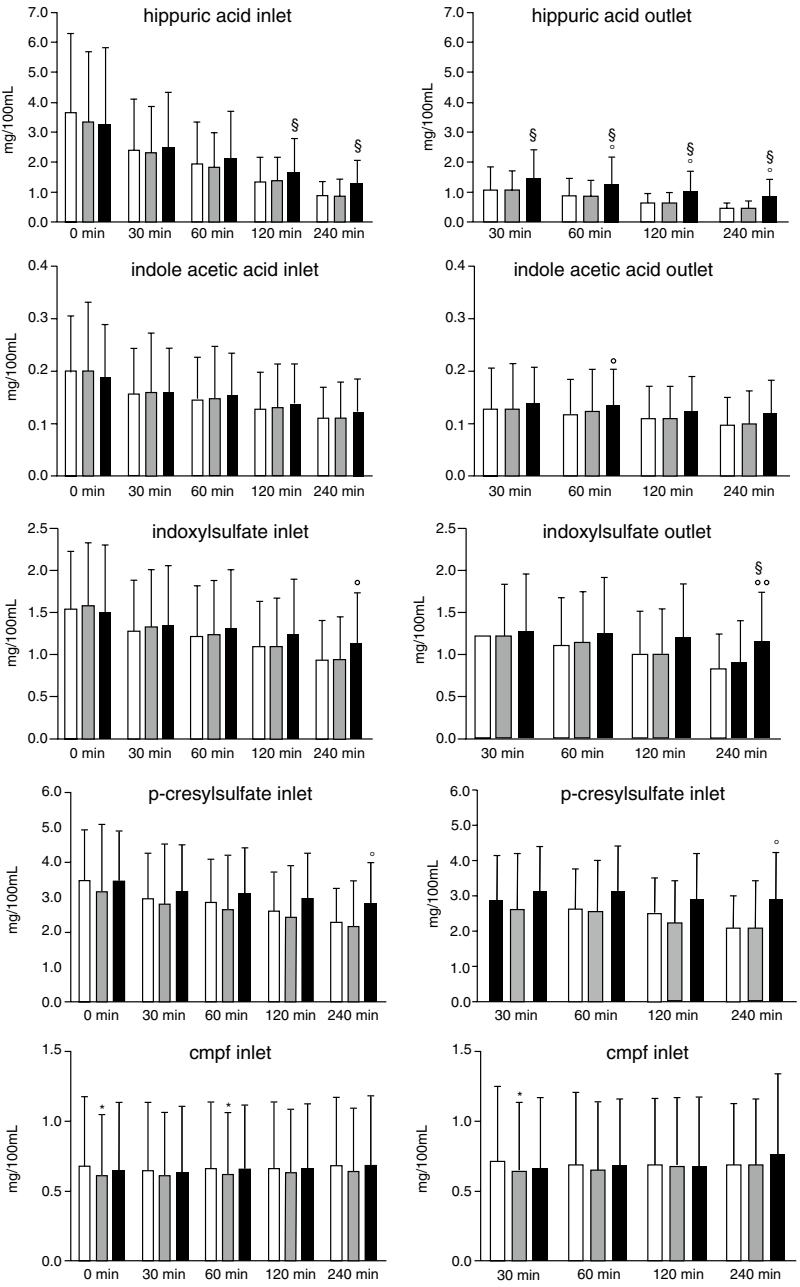


Fig. 14.1 Evolution of the inlet and outlet concentration of protein-bound compounds at different time points (0, 30, 60, 120 and 240 min). Post-dilution haemodiafiltration data are illustrated by *white bars*, pre-dilution haemodiafiltration data by *grey bars* and pre-dilution haemofiltration by *black bars*. *Pre-dilution haemodiafiltration versus post-dilution haemodiafiltration, °pre-dilution haemofiltration versus post-dilution haemodiafiltration, §pre-dilution haemofiltration versus pre-dilution haemodiafiltration; 1 symbol: $P<0.017$, 2 symbols: $P<0.001$ (Reprinted from Meert et al. [103]. With permission from Oxford University Press)

Compared with high-flux HD, an enhanced removal of p-cresol particularly in postdilution HDF was reported by Bammens and colleagues. In predilution HDF at high convective volumes, this beneficial effect was offset, probably because of impaired diffusion due to dilution of the blood entering the dialyzer [102]. Another study comparing postdilution HDF with predilution HDF at equivalent convective volume (i.e., 1:2), was unable to find a difference between the two treatment modes [103]. They determined reduction ratios of the protein-bound solutes pCS, IS, and IAA not exceeding 50 %, while HA was much more decreased by about 74 %, which must be attributed to lower protein-binding (Fig. 14.1). A more recent trial did also not confirm differences in protein-bound toxin removal between high-flux HD and postdilution HDF, demonstrating rather high reduction ratios of free and total pCS and IS hardly passing 50 % [73].

AGEs differ from the above mentioned small protein-bound toxins because of their heterogeneous molecular weight, covering a wide range. Accordingly, convective strategies seem to have a favourable effect on AGE removal, which is illustrated by 50 % and 300 % higher reduction ratios in online HDF (61.5 %) compared to high-flux HD (40.4 %) and low-flux HD (20.5 %), respectively [104].

The reduction ratios of various compounds are summarized in Table 14.1.

Influence of Modified Online HDF on Uremic Toxin Removal

Besides widely practiced predilution and postdilution HDF techniques, several modifications of HDF exist, which have shown to even further improve middle molecule removal, to achieve excellent middle molecule removal at reduced albumin loss or to allow safer operation conditions.

Mid-dilution HDF using a specific single cartridge dialyzer allows removal of middle molecules even exceeding that of postdilution HDF [105]. In the standard configuration, excessive blood inlet pressures were frequently observed, which led to the wide use in reverse mode without significant impairment of the treatment efficacy [106]. With regard to protein-bound toxin removal, mid-dilution HDF has no further advantage compared to postdilution HDF [107].

Online mixed-dilution HDF has shown to better preserve the dialyzer integrity than postdilution HDF by avoiding excessive hemoconcentration and dangerous pressure gradients [108]. At optimized flow rates controlled via TMP-ultrafiltration feedback, the clearance of β2M is improved, while the loss of albumin is reduced [109].

Other existing modifications of HDF do not qualify as online techniques because the substitution fluid is not infused in a controlled manner after ultrapure filtration. These techniques use the backfiltration of dialysate through the dialysis membrane as replacement fluid after excess forward-filtration of plasma water, thereby skipping redundancy as a safety feature in the ultrapure filtration process. Nevertheless, both push/pull HDF and double high-flux HDF achieve remarkably high middle molecule removal [110, 111].

Technical Limitations of Uremic Toxin Removal with Online HDF

The solute removal in convective dialysis techniques is linearly proportional to the substitution flow rate. Or in other words, best toxin removal is achieved at the highest feasible substitution flow rate. For predilution HDF, this increase is less steep and, hence, with respect to the substitution volume applied, less effective compared to postdilution HDF because of dilution of the blood and, thus, the solute concentrations entering the dialyzer. For equivalent clearance, the ultrafiltration rate needs to be at least two times greater for pre-dilution HDF compared with post-dilution [112]. In postdilution HDF, a critically high filtration fraction as a function of the convective flow rate (i.e., the sum of the substitution flow rate and the ultrafiltration flow rate set to achieve the patient's dry weight) exists. This filtration fraction puts the dialysis membrane at risk for clogging and may lead to an uncontrolled breakthrough of albumin, which passes the dialysis membrane in a controlled manner at lower flow rates [113, 114].

Despite being an essential protein associated with malnutrition, the maximum leakage of albumin during dialysis procedures is currently not defined [115]. In Japan, a limit of 4 g per session is recommended. This issue highlights the importance of choosing an appropriate dialyzer for HDF, which should represent a trade-off between maximum permeability for middle molecules and low leakage for albumin [115].

Teaching Points

- Uremic retention solutes are traditionally divided into small water-soluble compounds, middle molecules (MM) and protein-bound compounds
- Whereas small water-soluble compounds are removed by diffusion, MM are best removed by convection
- In online post-dilution HDF, diffusion of small water-soluble compounds is comparable to (high-flux) HD, while the removal of MM is markedly enhanced
- Removal of protein-bound uremic retention compounds, however, is not improved by HDF
- Intradialyzer clotting and albumin leakage may be rate limiting in high volume HDF

References

1. Duranton F, Cohen G, De Smet R, Rodriguez M, Jankowski J, Vanholder R, et al. Normal and pathologic concentrations of uremic toxins. J Am Soc Nephrol. 2012;23:1258–70.
2. Vanholder R, De Smet R, Glorieux G, Argiles A, Baurmeister U, Brunet P, et al. Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003;63(5):1934–43.

3. Boelaert J, t'Kindt R, Schepers E, Jorge L, Glorieux G, Neirynck N, et al. State-of-the-art non-targeted metabolomics in the study of chronic kidney disease. Metabolomics. 2014;10(3):425–42.
4. Weissinger EM, Kaiser T, Meert N, De Smet R, Walden M, Mischak H, et al. Proteomics: a novel tool to unravel the patho-physiology of uraemia. Nephrol Dial Transplant. 2004;19(12): 3068–77.
5. Vanholder R, Van Laecke S, Verbeke F, Glorieux G, Van Biesen W. Uraemic toxins and cardiovascular disease: in vitro research versus clinical outcome studies. Nephrol Dial Transplant Plus. 2008;1:2–10.
6. Vanholder R, Argiles A, Baurmeister U, Brunet P, Clark W, Cohen G, et al. Uremic toxicity: present state of the art. Int J Artif Organs. 2001;24(10):695–725.
7. Vanholder R, Van LS, Glorieux G. What is new in uremic toxicity? Pediatr Nephrol. 2008;23(8):1211–21.
8. Ledebo I. Principles and practice of hemofiltration and hemodiafiltration. Artif Organs. 1998;22(1):20–5.
9. Gupta BB, Jaffrin MY. In vitro study of combined convection- diffusion mass transfer in hemodialysers. Int J Artif Organs. 1984;7(5):263–8.
10. Evenepoel P, Rodriguez M, Ketteler M. Laboratory abnormalities in CKD-MBD: markers, predictors, or mediators of disease? Semin Nephrol. 2014;34(2):151–63.
11. Burke SK. Phosphate is a uremic toxin. J Ren Nutr. 2008;18(1):27–32.
12. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA. 2011;305(11):1119–27.
13. Chmielewski M, Cohen G, Wiecek A, Jesus CJ. The peptidic middle molecules: is molecular weight doing the trick? Semin Nephrol. 2014;34(2):118–34.
14. Wilson AM, Kimura E, Harada RK, Nair N, Narasimhan B, Meng XY, et al. Beta2-microglobulin as a biomarker in peripheral arterial disease: proteomic profiling and clinical studies. Circulation. 2007;116(12):1396–403.
15. Saijo Y, Utsugi M, Yoshioka E, Horikawa N, Sato T, Gong Y, et al. Relationship of beta2-microglobulin to arterial stiffness in Japanese subjects. Hypertens Res. 2005;28(6): 505–11.
16. Ripoll E, Revilla M, Hernandez ER, Arribas I, Villa LF, Rico H. New evidence that serum beta(2)-microglobulin behaves as a biological marker of bone remodelling in women. Eur J Clin Invest. 1996;26(8):681–5.
17. Cheung AK, Rocco MV, Yan G, Leypoldt JK, Levin NW, Greene T, et al. Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. J Am Soc Nephrol. 2006;17(2):546–55.
18. Cheung AK, Greene T, Leypoldt JK, Yan G, Allon M, Delmez J, et al. Association between serum 2-microglobulin level and infectious mortality in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3(1):69–77.
19. Kuragano T, Kida A, Furuta M, Nanami M, Otaki Y, Hasuike Y, et al. The impact of beta2-microglobulin clearance on the risk factors of cardiovascular disease in hemodialysis patients. ASAIO J. 2010;56(4):326–32.
20. Liabeuf S, Lenglet A, Desjardins L, Neirynck N, Glorieux G, Lemke HD, et al. Plasma beta-2 microglobulin is associated with cardiovascular disease in uremic patients. Kidney Int. 2012;82(12):1297–303.
21. Neirynck N, Glorieux G, Boelaert J, Schepers E, Liabeuf S, Dhondt A, et al. Uremia-related oxidative stress in leukocytes is not triggered by beta2-microglobulin. J Ren Nutr. 2013;23(6):456–63.
22. Cheung CL, Lam KS, Cheung BM. Serum beta-2 microglobulin predicts mortality in people with diabetes. Eur J Endocrinol. 2013;169(1):1–7.
23. Raikou VD, Tentolouris N, Kyriaki D, Evaggelatou A, Tzanatou H. beta2-Microglobulin, pulse pressure and metabolic alterations in hemodialysis patients. Nephron Clin Pract. 2011;117(3):c237–45.

24. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrol. 2012;7(12):1938–46.
25. Adesso S, Popolo A, Bianco G, Sorrentino R, Pinto A, Autore G, et al. The uremic toxin indoxyl sulphate enhances macrophage response to LPS. PLoS One. 2013;8(9): e76778.
26. Glorieux GL, Dhondt AW, Jacobs P, Van LJ, Lameire NH, De Deyn PP, et al. In vitro study of the potential role of guanidines in leukocyte functions related to atherogenesis and infection. Kidney Int. 2004;65(6):2184–92.
27. Schepers E, Barreto DV, Liabeuf S, Glorieux G, Eloot S, Barreto FC, et al. Symmetric dimethylarginine as a proinflammatory agent in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(10):2374–83.
28. Bemelmans MH, Gouma DJ, Buurman WA. Influence of nephrectomy on tumor necrosis factor clearance in a murine model. J Immunol. 1993;150(5):2007–17.
29. Garibotto G, Sofia A, Balbi M, Procopio V, Villaggio B, Tarroni A, et al. Kidney and splanchnic handling of interleukin-6 in humans. Cytokine. 2007;37(1):51–4.
30. Neirynck N, Glorieux G, Schepers E, Dhondt A, Verbeke F, Vanholder R. Pro-inflammatory cytokines and leukocyte oxidative burst in chronic kidney disease: culprits or innocent bystanders? Nephrol Dial Transplant. 2015;30(6):943–51.
31. Barreto DV, Barreto FC, Liabeuf S, Temmar M, Lemke HD, Tribouilloy C, et al. Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease. Kidney Int. 2010;77(6):550–6.
32. Kimmel PL, Phillips TM, Simmens SJ, Peterson RA, Weihs KL, Alleyne S, et al. Immunologic function and survival in hemodialysis patients. Kidney Int. 1998;54(1):236–44.
33. Stenvinkel P, Ketteler M, Johnson RJ, Lindholm B, Pecoits-Filho R, Riella M, et al. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia – the good, the bad, and the ugly. Kidney Int. 2005;67(4):1216–33.
34. Girndt M, Kaul H, Sester U, Ulrich C, Sester M, Georg T, et al. Anti-inflammatory interleukin-10 genotype protects dialysis patients from cardiovascular events. Kidney Int. 2002;62(3): 949–55.
35. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol. 2007;18(9):2600–8.
36. Seiler S, Cremers B, Rebling NM, Hornof F, Jeken J, Kersting S, et al. The phosphatonin fibroblast growth factor 23 links calcium-phosphate metabolism with left-ventricular dysfunction and atrial fibrillation. Eur Heart J. 2011;32(21):2688–96.
37. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–92.
38. Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 2009;119(19):2545–52.
39. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011;121(11):4393–408.
40. Pascual M, Steiger G, Estreicher J, Macon K, Volanakis JE, Schifferli JA. Metabolism of complement factor D in renal failure. Kidney Int. 1988;34(4):529–36.
41. Volanakis JE, Barnum SR, Giddens M, Galla JH. Renal filtration and catabolism of complement protein D. N Engl J Med. 1985;312(7):395–9.
42. Pascual M, Paccaud JP, Macon K, Volanakis JE, Schifferli JA. Complement activation by the alternative pathway is modified in renal failure: the role of factor D. Clin Nephrol. 1989; 32(4):185–93.
43. Balke N, Holtkamp U, Horl WH, Tschesche H. Inhibition of degranulation of human polymorphonuclear leukocytes by complement factor D. FEBS Lett. 1995;371(3):300–2.
44. Sirich T, Meyer TW. Indoxyl sulfate: long suspected but not yet proven guilty. Clin J Am Soc Nephrol. 2011;6(1):3–4.

45. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review. J Am Soc Nephrol. 2014;25(9):1897–907.
46. Barreto FC, Barreto DV, Liabeuf S, Meert N, Glorieux G, Temmar M, et al. Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. Clin J Am Soc Nephrol. 2009;4(10):1551–8.
47. Chiu CA, Lu LF, Yu TH, Hung WC, Chung FM, Tsai IT, et al. Increased levels of total P-Cresylsulphate and indoxyl sulphate are associated with coronary artery disease in patients with diabetic nephropathy. Rev Diabet Stud. 2010;7(4):275–84.
48. Liabeuf S, Barreto DV, Barreto FC, Meert N, Glorieux G, Schepers E, et al. Free p-cresylsulphate is a predictor of mortality in patients at different stages of chronic kidney disease. Nephrol Dial Transplant. 2010;25(4):1183–91.
49. Wang CP, Lu LF, Yu TH, Hung WC, Chiu CA, Chung FM, et al. Serum levels of total p-cresylsulphate are associated with angiographic coronary atherosclerosis severity in stable angina patients with early stage of renal failure. Atherosclerosis. 2010;211(2):579–83.
50. Wu IW, Hsu KH, Lee CC, Sun CY, Hsu HJ, Tsai CJ, et al. p-Cresyl sulphate and indoxyl sulphate predict progression of chronic kidney disease. Nephrol Dial Transplant. 2011;26(3):938–47.
51. Wu IW, Hsu KH, Hsu HJ, Lee CC, Sun CY, Tsai CJ, et al. Serum free p-cresyl sulfate levels predict cardiovascular and all-cause mortality in elderly hemodialysis patients – a prospective cohort study. Nephrol Dial Transplant. 2012;27(3):1169–75.
52. Pletinck A, Glorieux G, Schepers E, Cohen G, Gondouin B, Van LM, et al. Protein-bound uremic toxins stimulate crosstalk between leukocytes and vessel wall. J Am Soc Nephrol. 2013;24(12):1981–94.
53. Kim YH, Kwak KA, Gil HW, Song HY, Hong SY. Indoxyl sulfate promotes apoptosis in cultured osteoblast cells. BMC Pharmacol Toxicol. 2013;14:60.
54. Barnes KJ, Rowland A, Polasek TM, Miners JO. Inhibition of human drug-metabolising cytochrome P450 and UDP-glucuronosyltransferase enzyme activities in vitro by uremic toxins. Eur J Clin Pharmacol. 2014;70(9):1097–106.
55. Sun CY, Young GH, Hsieh YT, Chen YH, Wu MS, Wu VC, et al. Protein-bound uremic toxins induce tissue remodeling by targeting the EGF receptor. J Am Soc Nephrol. 2015;26(2):281–90.
56. Ng HY, Yisireyili M, Saito S, Lee CT, Adelibieke Y, Nishijima F, et al. Indoxyl sulfate downregulates expression of Mas receptor via OAT3/AhR/Stat3 pathway in proximal tubular cells. PLoS One. 2014;9(3):e91517.
57. Sirich TL, Meyer TW, Gondouin B, Brunet P, Niwa T. Protein-bound molecules: a large family with a bad character. Semin Nephrol. 2014;34(2):106–17.
58. Jourde-Chiche N, Dou L, Sabatier F, Calaf R, Cerini C, Robert S, et al. Levels of circulating endothelial progenitor cells are related to uremic toxins and vascular injury in hemodialysis patients. J Thromb Haemost. 2009;7(9):1576–84.
59. Dou L, Sallee M, Cerini C, Poitevin S, Gondouin B, Jourde-Chiche N, et al. The cardiovascular effect of the uremic solute indole-3 acetic acid. J Am Soc Nephrol. 2015;26(4):876–87.
60. Chitalia VC, Shivanna S, Martorell J, Balcells M, Bosch I, Kolandaivelu K, et al. Uremic serum and solutes increase post-vascular interventional thrombotic risk through altered stability of smooth muscle cell tissue factor. Circulation. 2013;127(3):365–76.
61. Gondouin B, Cerini C, Dou L, Sallee M, Duval-Sabatier A, Pletinck A, et al. Indolic uremic solutes increase tissue factor production in endothelial cells by the aryl hydrocarbon receptor pathway. Kidney Int. 2013;84(4):733–44.
62. Lees HJ, Swann JR, Wilson ID, Nicholson JK, Holmes E. Hippurate: the natural history of a mammalian-microbial cometabolite. J Proteome Res. 2013;12(4):1527–46.
63. Satoh M, Hayashi H, Watanabe M, Ueda K, Yamato H, Yoshioka T, et al. Uremic toxins overload accelerates renal damage in a rat model of chronic renal failure. Nephron Exp Nephrol. 2003;95(3):e111–8.
64. Mutsaers HA, van den Heuvel LP, Ringens LH, Dankers AC, Russel FG, Wetzels JF, et al. Uremic toxins inhibit transport by breast cancer resistance protein and multidrug resistance protein 4 at clinically relevant concentrations. PLoS One. 2011;6(4):e18438.

65. Cohen G, Raupachova J, Wimmer T, Deicher R, Horl WH. The uraemic retention solute parahydroxy-hippuric acid attenuates apoptosis of polymorphonuclear leukocytes from healthy subjects but not from haemodialysis patients. Nephrol Dial Transplant. 2008;23(8):2512–9.
66. Glorieux G, Helling R, Henle T, Brunet P, Deppisch R, Lameire N, et al. In vitro evidence for immune activating effect of specific AGE structures retained in uremia. Kidney Int. 2004; 66(5):1873–80.
67. Uribarri J, Stirban A, Sander D, Cai W, Negrean M, Buenting CE, et al. Single oral challenge by advanced glycation end products acutely impairs endothelial function in diabetic and nondiabetic subjects. Diabetes Care. 2007;30(10):2579–82.
68. Suliman ME, Heimburger O, Barany P, Anderstam B, Pecoits-Filho R, Rodriguez AE, et al. Plasma pentosidine is associated with inflammation and malnutrition in end-stage renal disease patients starting on dialysis therapy. J Am Soc Nephrol. 2003;14(6):1614–22.
69. Rodriguez-Ayala E, Anderstam B, Suliman ME, Seeberger A, Heimburger O, Lindholm B, et al. Enhanced RAGE-mediated NFkappaB stimulation in inflamed hemodialysis patients. Atherosclerosis. 2005;180(2):333–40.
70. Nakashima A, Carrero JJ, Qureshi AR, Miyamoto T, Anderstam B, Barany P, et al. Effect of circulating soluble receptor for advanced glycation end products (sRAGE) and the proinflammatory RAGE ligand (EN-RAGE, S100A12) on mortality in hemodialysis patients. Clin J Am Soc Nephrol. 2010;5(12):2213–9.
71. Mallipattu SK, He JC, Uribarri J. Role of advanced glycation endproducts and potential therapeutic interventions in dialysis patients. Semin Dial. 2012;25(5):529–38.
72. Ficheux A, Argiles A, Mion H, Mion CM. Influence of convection on small molecule clearances in online hemodiafiltration. Kidney Int. 2000;57(4):1755–63.
73. Krieter DH, Hackl A, Rodriguez A, Chenine L, Moragues HL, Lemke HD, et al. Protein-bound uraemic toxin removal in haemodialysis and post-dilution haemodiafiltration. Nephrol Dial Transplant. 2010;25(1):212–8.
74. Maduell F, Navarro V, Cruz MC, Torregrosa E, Garcia D, Simon V, et al. Osteocalcin and myoglobin removal in on-line hemodiafiltration versus low- and high-flux hemodialysis. Am J Kidney Dis. 2002;40(3):582–9.
75. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. J Am Soc Nephrol. 2000;11(12):2344–50.
76. Ahrenholz P, Winkler RE, Ramlow W, Tiess M, Muller W. On-line hemodiafiltration with pre- and postdilution: a comparison of efficacy. Int J Artif Organs. 1997;20(2):81–90.
77. Ficheux A, Argiles A, Bosc JY, Mion C. Analysis of the influence of the infusion site on dialyser clearances measured in an in vitro system mimicking haemodialysis and haemodiafiltration. Blood Purif. 1999;17(1):10–8.
78. Spalding EM, Chamney PW, Farrington K. Phosphate kinetics during hemodialysis: evidence for biphasic regulation. Kidney Int. 2002;61(2):655–67.
79. Cornelis T, van der Sande FM, Eloot S, Cardinaels E, Bekers O, Damoiseaux J, et al. Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. Am J Kidney Dis. 2014;64(2):247–56.
80. Minutolo R, Bellizzi V, Cioffi M, Iodice C, Giannattasio P, Andreucci M, et al. Postdialytic rebound of serum phosphorus: pathogenetic and clinical insights. J Am Soc Nephrol. 2002;13(4):1046–54.
81. Zehnder C, Gutzwiller JP, Renggli K. Hemodiafiltration – a new treatment option for hyperphosphatemia in hemodialysis patients. Clin Nephrol. 1999;52(3):152–9.
82. Penne EL, van der Weerd NC, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55(1):77–87.
83. Oates T, Pinney JH, Davenport A. Haemodiafiltration versus high-flux haemodialysis: effects on phosphate control and erythropoietin response. Am J Nephrol. 2011;33(1):70–5.

84. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
85. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
86. Wang AY, Lai KN. The importance of residual renal function in dialysis patients. Kidney Int. 2006;69(10):1726–32.
87. Henderson L. Biophysics of ultrafiltration and hemofiltration. In: Jacobs C, Kjellstrand C, Koch K, Winchester J, editors. Replacement of renal function by dialysis. 4th ed. Dordrecht: Kluwer Academic Publisher; 1996. p. 114–45.
88. Kazama JJ, Maruyama H, Gejyo F. Reduction of circulating beta2-microglobulin level for the treatment of dialysis-related amyloidosis. Nephrol Dial Transplant. 2001;16 Suppl 4:31–5.
89. Lin CL, Yang CW, Chiang CC, Chang CT, Huang CC. Long-term on-line hemodiafiltration reduces predialysis beta-2-microglobulin levels in chronic hemodialysis patients. Blood Purif. 2001;19(3):301–7.
90. Lornoy W, Becaus I, Billiouw JM, Sierens L, Van MP, D'Haenens P. On-line haemodiafiltration. Remarkable removal of beta2-microglobulin. Long-term clinical observations. Nephrol Dial Transplant. 2000;15 Suppl 1:49–54.
91. Lornoy W, Becaus I, Billiouw JM, Sierens L, Van MP. Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. Am J Nephrol. 1998;18(2):105–8.
92. Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. Nephrol Dial Transplant. 2000;15 Suppl 1: 43–8.
93. Penne EL, van der Weerd NC, Blankestijn PJ, van den Dorpel MA, Grooteman MP, Nube MJ, et al. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. Clin J Am Soc Nephrol. 2010;5(1): 80–6.
94. Fry AC, Singh DK, Chandna SM, Farrington K. Relative importance of residual renal function and convection in determining beta-2-microglobulin levels in high-flux haemodialysis and on-line haemodiafiltration. Blood Purif. 2007;25(3):295–302.
95. Gil C, Lucas C, Possante C, Jorge C, Gomes F, Candeias M, et al. On-line haemodiafiltration decreases serum TNFalpha levels in haemodialysis patients. Nephrol Dial Transplant. 2003;18(2):447–8.
96. Chancharoenthana W, Tiranathanagul K, Srisawat N, Susantitaphong P, Leelahavanichkul A, Praditpornsilpa K, et al. Enhanced vascular endothelial growth factor and inflammatory cytokine removal with online hemodiafiltration over high-flux hemodialysis in sepsis-related acute kidney injury patients. Ther Apher Dial. 2013;17(5):557–63.
97. Patrier L, Dupuy AM, Granger VA, Chalabi L, Morena M, Canaud B, et al. FGF-23 removal is improved by on-line high-efficiency hemodiafiltration compared to conventional high flux hemodialysis. J Nephrol. 2013;26(2):342–9.
98. Lesaffer G, De Smet SR, Lameire N, Dhondt A, Duym P, Vanholder R. Intradialytic removal of protein-bound uraemic toxins: role of solute characteristics and of dialyser membrane. Nephrol Dial Transplant. 2000;15(1):50–7.
99. Martinez AW, Recht NS, Hostetter TH, Meyer TW. Removal of P-cresol sulfate by hemodialysis. J Am Soc Nephrol. 2005;16(11):3430–6.
100. Meyer TW, Leeper EC, Bartlett DW, Depner TA, Lit YZ, Robertson CR, et al. Increasing dialysate flow and dialyzer mass transfer area coefficient to increase the clearance of protein-bound solutes. J Am Soc Nephrol. 2004;15(7):1927–35.
101. Meyer TW, Walther JL, Pagtalunan ME, Martinez AW, Torkamani A, Fong PD, et al. The clearance of protein-bound solutes by hemofiltration and hemodiafiltration. Kidney Int. 2005;68(2):867–77.

102. Bammens B, Evenepoel P, Verbeke K, Vanrenterghem Y. Removal of the protein-bound solute p-cresol by convective transport: a randomized crossover study. Am J Kidney Dis. 2004;44(2):278–85.
103. Meert N, Eloot S, Waterloos MA, Van LM, Dhondt A, Glorieux G, et al. Effective removal of protein-bound uraemic solutes by different convective strategies: a prospective trial. Nephrol Dial Transplant. 2009;24(2):562–70.
104. Lin CL, Huang CC, Yu CC, Yang HY, Chuang FR, Yang CW. Reduction of advanced glycation end product levels by on-line hemodiafiltration in long-term hemodialysis patients. Am J Kidney Dis. 2003;42(3):524–31.
105. Krieter DH, Falkenhain S, Chalabi L, Collins G, Lemke HD, Canaud B. Clinical cross-over comparison of mid-dilution hemodiafiltration using a novel dialyzer concept and post-dilution hemodiafiltration. Kidney Int. 2005;67(1):349–56.
106. Pedrini LA, Feliciani A, Zerbi S, Cozzi G, Ruggiero P. Optimization of mid-dilution haemodiafiltration: technique and performance. Nephrol Dial Transplant. 2009;24(9):2816–24.
107. Eloot S, Dhondt A, Van LM, Waterloos MA, Vanholder R. Removal of water-soluble and protein-bound solutes with reversed mid-dilution versus post-dilution haemodiafiltration. Nephrol Dial Transplant. 2012;27(8):3278–83.
108. Pedrini LA, De Cristofaro V, Pagliari B, Sama F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000;58(5): 2155–65.
109. Pedrini LA, De Cristofaro V. On-line mixed hemodiafiltration with a feedback for ultrafiltration control: effect on middle-molecule removal. Kidney Int. 2003;64(4):1505–13.
110. Shinzato T, Miwa M, Nakai S, Takai I, Matsumoto Y, Morita H, et al. Alternate repetition of short fore- and backfiltrations reduces convective albumin loss. Kidney Int. 1996;50(2): 432–5.
111. Tiranathanagul K, Yossundharakul C, Techawathanawanna N, Katavetin P, Hanvivatvong O, Praditpornsilp K, et al. Comparison of middle-molecule clearance between convective control double high-flux hemodiafiltration and on-line hemodiafiltration. Int J Artif Organs. 2007;30(12):1090–7.
112. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28(3):542–50.
113. Ahrenholz PG, Winkler RE, Michelsen A, Lang DA, Bowry SK. Dialysis membrane-dependent removal of middle molecules during hemodiafiltration: the beta2-microglobulin/albumin relationship. Clin Nephrol. 2004;62(1):21–8.
114. Krieter DH, Martin K, Reinhardt B, Sauer N, Lemke HD, Leray Moragues H, et al. Low-molecular weight protein removal of the new DIAPES® HF800XP membrane in postdilutional hemodiafiltration. J Am Soc Nephrol. 2002;13 suppl:238A
115. Krieter DH, Canaud B. High permeability of dialysis membranes: what is the limit of albumin loss? Nephrol Dial Transplant. 2003;18(4):651–4.

Chapter 15
Effects of Hemodiafiltration on Platelets and Coagulation

Menso J. Nubé and Auguste Sturk

Abstract In patients with chronic kidney disease (CKD) the hemostatic balance is disturbed due to alterations in the coagulation cascade, inhibitors of the coagulation system, the fibrinolytic pathway, platelets and endothelial cells. As a result, CKD is characterized by both a bleeding tendency and a pro-thrombotic state. In hemodialysis (HD) patients, coagulation is activated during the passage of blood through the extra-corporeal circuit, which depends largely on the type of dialyzer and individual patient characteristics. Furthermore, platelets are stimulated and release their granule contents. With the exception of the platelet degranulation product beta-thromboglobulin, treatment-induced alterations in hemostatic parameters are more pronounced during HDF than HD, most probably due to a higher trans-membrane pressure (TMP) and increased hemoconcentration. In clinical practice, the required doses of both unfractionated heparin and low molecular weight heparin are higher during HDF as compared to HD.

Keywords Hemodialysis • Hemodiafiltration • Clotting • Platelets • Platelet surface marker CD62p • Thromboglobulin • Platelet factor 4 • Heparin

Introduction

Patients with chronic kidney diseases (CKD) develop a variety of hemostatic disorders during the course of their disease. Actually, derangements in opposite directions occur, as both the tendency for bleeding and clotting are increased in these patients. The underlying abnormalities include all components of the hemostatic system, i.e. the coagulation cascade, inhibitors of coagulation, the fibrinolytic

M.J. Nubé, MD, PhD (✉)
Department of Nephrology, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081HV, The Netherlands
e-mail: mensonube@gmail.com

A. Sturk, PhD
Department of Clinical Chemistry, Academic Medical Center, Amsterdam, The Netherlands

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_15

pathway, platelets and endothelial cells, which are influenced by uremic toxins and metabolic substances accumulating in renal insufficiency [1–3]. When renal failure progresses to end-stage kidney-disease (ESKD), renal replacement therapy becomes necessary for survival. During treatment with hemodialysis (HD), the blood of the patients is exposed to the foreign materials of the extra-corporeal circuit (ECC), consisting of needles, blood lines, air bubble trap and dialyzer. In addition, blood components are subjected to the mechanical forces of the roller pump and the transmembrane pressure (TMP) within the dialyzer needed for ultrafiltration (UF). Finally, anticoagulants are administered intravenously to prevent clotting over the entire length of the ECC, especially at the dialyzer because of the large surface area and high TMP. As a result of UF, blood viscosity progressively increases during the treatment session, which may also contribute to the susceptibility for clotting. All these factors may further influence the already disturbed hemostatic balance in patients with CKD. As both TMP and hemoconcentration during postdilution hemodiafiltration (HDF) are considerable higher as compared to HD [4], it is conceivable that hemostasis is even further deranged during HDF.

Platelet Activation

Compared to healthy controls, ESKD patients have a low platelet count at the start of HD treatment. This declines even further during first passage through the extracorporeal circuit (ECC), most probably due to adherence of platelets onto the dialyzer membrane [5, 6]. Especially the fraction of immature platelets is decreased, suggesting reduced megakaryopoiesis as a cause for the low platelet number, which will be further reduced by HD.

During HD, platelets are activated, as indicated by an early upregulation of the platelet surface marker p-selectin (CD62p) [7]. Moreover, small deviations are observed in mean platelet volume, platelet distribution width and platelet large cell ration, suggesting degranulation and/or an altered balance between old (small) and young (large) platelets [6]. Electron microscopic evaluation of a blood sample from a chronic HD patient taken before the start of treatment indeed showed that the surface area of platelets is considerably smaller as compared to platelets from a healthy subject. The total area of the platelet granules called dense bodies, which contain serotonin, histamine, pyrophosphate and other low molecular weight secretion products, was also noticeably reduced as quantified by application of digital image masks (Fig. 15.1) [8]. Together, these findings suggest severe depletion of the platelet granular content, most probably as a result of the repeated dialysis treatment, which reduces their capability to function in the hemostatic process.

Release of the platelet granule content can also be estimated by measuring platelet degranulation products, such as platelet factor 4 (PF4) and beta-thromboglobulin (BTG), in the plasma. These constituents as well as all other proteins secreted by the platelet upon their activation, are localized in the so-called α-granules of the platelet. From a cross-over analysis in eight chronic HD patients who were treated

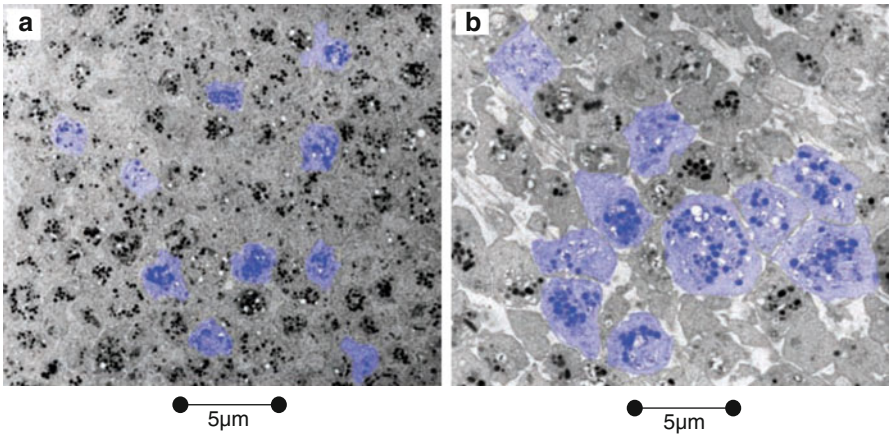


Fig. 15.1 Digital masks of electron microscopic platelet evaluation of (**a**) a HD subject and (**b**) a healthy subject. Masks are shown in *blue*. Magnification: 2500× (Reprinted from Schoorl et al. [8]. With permission from Page Press)

alternatively with unfractionated heparin (UHep), low molecular weight heparin (LMWH) or citrate during the HD procedure, it appeared that degranulation was absent during treatment with citrate but did occur with UHep and LMWH, while differences between UHep and LMWH were not observed [9]. Of note, when LMWH was administered 10 min before the start of HD, a considerable increase in PF4 was observed, while CD62p expression and BTG levels remained unaltered. After starting dialysis, CD62p expression and BTG levels showed a marked rise, while PF4 values hardly increased any further. From this study it also appeared that the increase in CD62p expression correlated with both the drop in platelet count after first passage and BTG release. Thus, treatment-induced PF4 release depends rather on heparin administration than on extracorporeal circulation and originates primarily from non-platelet derived sources, such as endothelial proteoglycans [10], and is therefore not correlated with CD62p expression on the platelet surface. By contrast, the HD-induced increase in plasma BTG levels is not affected by the administration of LMWH, but originates from platelets partially releasing their granular content during their activation in the extracorporeal circuit and is therefore highly correlated with the expression of CD62p. This platelet surface marker originates from the membrane of the α-granules and becomes exposed on the platelet surface by the fusion of that membrane with the outer membrane of the platelet during the secretory process.

Taking these findings in mind, in a subgroup of CONTRAST, platelet activation was compared between nine patients who were treated with online post-dilution HDF and ten with low-flux HD [4]. From this study it appeared that the expression of CD62p was more pronounced and more protracted during HDF (Fig. 15.2). Moreover, the drop in platelet counts in the first 30 min and the rebound after 1 h was significantly greater during this mode of treatment.

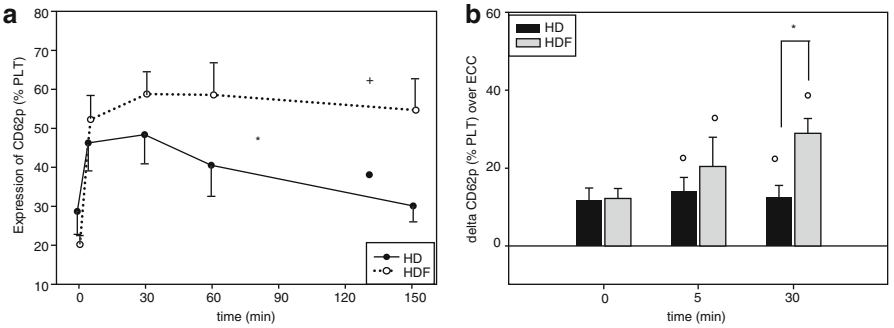


Fig. 15.2 (**a**) Platelet CD62p expression (% platelets with increased surface expression, PLT, mean ± SE) in the efferent line during HD and HDF. Changes over time were observed during both treatments: • (HD) and + (HDF): P<0.001. Difference between HD and HDF: ∗P=0.002. (**b**) Changes in PLT CD62p expression (% PLT, mean ± SE) over the ECC (delta: efferent value – afferent value) during HD and HDF: °P<0.05. Difference between HD and HDF: ∗P=0.039 (Reprinted from Gritters-van den Oever et al. [4]. With permission from Oxford University Press)

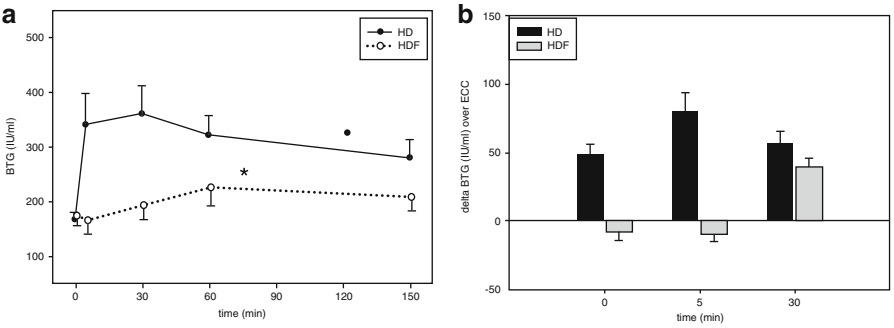


Fig. 15.3 (**a**) Plasma BTG (IU/ml, mean ± SE) concentrations in the efferent line during HD and HDF. Changes over time were observed during HD: • P=0.013. Difference between HD and HDF: *P=0.030. (**b**) Changes in BTG (IU/ml, mean ± SE) concentrations over the ECC (delta: efferent value –afferent value) during HD and HDF (Reprinted from Gritters-van den Oever et al. [4]. With permission from Oxford University Press)

As for the degranulation product PF4 (MW 29 kD), only minor differences were observed between HD and HDF, which is in line with the observation that its increase during the treatment is mainly due to LMWH-induced detachment from the endothelium. Considering BTG, however, a completely different picture emerged. In a previous study in patients who were dialyzed with low-flux HD, it was already found that BTG is almost exclusively released within the ECC [11]. In that study, BTG levels rose almost twofold over the dialyzer, with a maximum after 30 min. At the end of HD, blood levels in the arterial line were still elevated. During HDF however, BTG levels hardly changed, both over the ECC and over time (Fig. 15.3).

As the molecular weight of BTG is 36 kilo Dalton (kD), it is plausible that this substance is removed by convection during HDF, which is obvious not the case in

low-flux HD. Alternatively, it is conceivable that platelets are exhausted as a result of the repetitive stimulation by HDF treatment, and hence, incapable of further secreting granule contents. The combined data from HD and HDF patients showed a highly significant correlation between the hemoconcentration (during HDF up to 49 %) on the one hand and a drop in platelet numbers ($r=-0.82$) or platelet activation ($r=0.68$), as measured by CD62p expression, at the other. Lastly, as TMP values appeared approximately three times higher in HDF than in HD, the high pressure gradient over the dialyzer may also contribute to platelet activation [4].

Altogether, from these data it appears that, while platelet activation occurs to a similar extent during low-flux and high-flux HD [12], it is more pronounced during HDF. Both activation and trapping within the ECC are correlated with the extent of hemoconcentration within the dialyzer. It is currently unknown, however, whether the chronic platelet activation by HDF treatment is more harmful to the patients than the degree of platelet stimulation by HD. As activated platelets adhere to both intact and activated endothelium and may thus contribute to the process of atherosclerosis [13], depletion by exhaustion may prevent or delay platelets from their involvement in this process.

Activation of Coagulation

Introduction

Coagulation is generally divided into the intrinsic pathway, initiated by contact of the blood with negatively charged surfaces and leading to activated coagulation factor XII (XIIa), and the extrinsic pathway initiated by tissue factor (TF), which is exposed at sites of vascular injury and activates the coagulation system via factor VII (VIIa). Both pathways activate factor X (Xa), which together with activated factor V (Va) is capable of converting prothrombin into thrombin. Once formed, thrombin converts fibrinogen to fibrin monomers, which polymerize to form stable fibrin strands. Finally, a three dimensional network is formed by interaction of thrombin-induced factor XIII activation (XIIIa). Calcium is a cofactor required at several phases of these activation processes. The coagulation cascade is regulated by several inhibitory mechanisms, including antithrombin (AT), the protein C system and the TF pathway inhibitor (TFPI). Once a clot is formed its proteolytic degradation occurs, exerted by the plasmin system, finally leading to fibrin and thrombus dissolution (Fig. 15.4).

In HD patients, the clotting cascade is activated once the blood interacts with the ECC. Without anticoagulation, this would lead to clot formation, obstruction of the dialyzer and a reduction in the effectiveness of the dialysis procedure. In clinical practice, the tendency for clotting is reduced by the intravenous administration of unfractionated heparin (UHep) or low molecular weight heparin (LMWH). UHep inhibits the coagulation cascade by inducing a conformational change in the enzyme inhibitor AT that results in its binding to thrombin, leading to thrombin-antithrombin

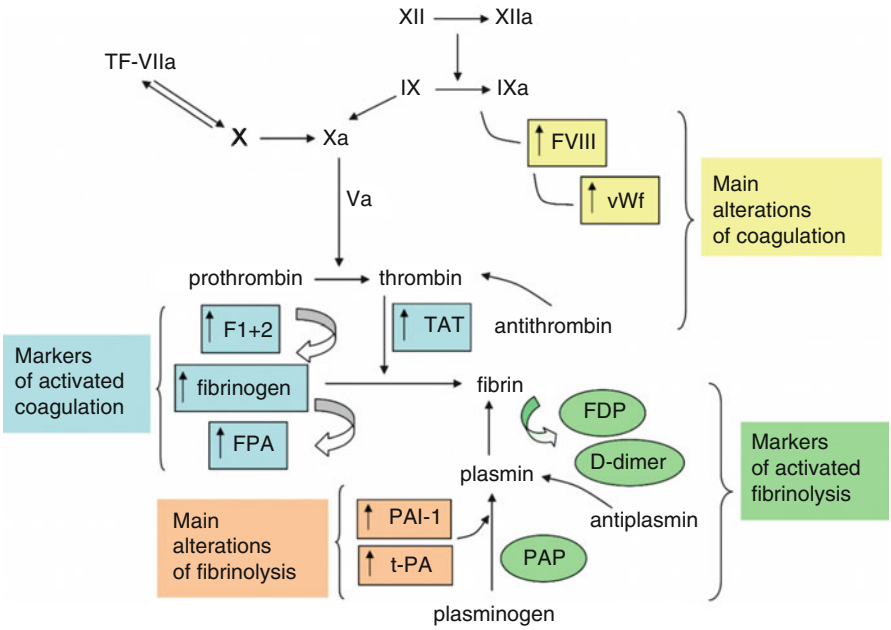


Fig. 15.4 Markers of activated coagulation and fibrinolysis together with main alterations of coagulation and fibrinolysis in the cause of HD treatment [14]. Abbreviations: *F1 + 2* prothrombin fragment FI+2, the peptide originating from the prothrombin molecule upon its proteolytic conversion into thrombin, *FPA* fibrinopeptide A, one of the peptides originating from fibrinogen upon its proteolytic conversion into the fibrin monomr, *PAI-1* plasminogen activator inhibitor, *PAP* plasmin-antiplasmin complexes, *TAT* thrombin-antithrombin complexes, *t-PA* tissue type plasminogen activator, *vWf* von Willebrand factor (Modified from Miljic et al. [14]. With permission from Hormones Journal)

complexes (TAT) with inactivated thrombin, and thereby inhibition of fibrin formation. By contrast, LMWH almost exclusively inhibits activation of factor X to Xa. In the following subparagraphs, the status of the coagulation system is generally estimated by measuring different steps in the coagulation cascade, such as factor X and Xa, TAT complexes, the prothrombin fragment F1+2, the immediate precursor of insoluble fibrin named thrombus precursor protein (TpP) and the fibrin degradation product D-dimer.

Activation of Coagulation in End-Stage Kidney Disease (ESKD)

Despite a compromised platelet function and a hemorrhagic tendency, uremic patients not yet on dialysis are generally characterized by a pro-coagulant state, as measured by increased plasma concentrations of fibrinogen, D-dimer, increased prothrombin fragment 1+2, tissue factor (TF) antigen, coagulation factor VII, and reductions in the levels of antithrombine, protein S and factor X [13, 15–17].

During HD a complex interaction occurs between the hemostatic system and the ECC, which depends on individual characteristics of the patient and the membrane material of the dialyzer. As already mentioned, anticoagulants are administered directly at the start of the treatment to prevent clotting. From a number of studies in HD patients who were treated with different membranes, it was concluded that HD patients already show signs of coagulation activation before treatment, as measured by increased concentrations of the prothrombin fragment F1+2. Studies on dialyzers with different membranes [polyacrylonitrile (AN69), polymethylmethacrylate (PMMA) and polysulphon (PS)], all showed a decrease of factor XII levels over time, which, however, depended highly on the material of the membranes used (PMMA: mean decrease 80 % of the initial value, PS: mean 40 % and AN69: mean 28 %). Plasma TpP levels, a measure of fibrin clot formation, remained unaltered during HD with PS membranes and showed an increase during treatment with both AN69 and PMMA dialyzers [18, 19]. Comparable findings were obtained for the coagulation activation marker F1+2. TAT complexes remained unaltered during HD with PMMA, but peaked sharply after 30 min during treatment with both AN69 and PS. All measurements showed large inter-individual variations. Of note, some of these intra-dialytic changes (TAT, F1+2) can easily be missed when measuring only before and after a session, as return of these parameters to pre-dialytic values may occur towards the end of the treatment [16, 20].

Altogether, it can be concluded that the coagulation system in patients with ESKD is already activated prior to the start of HD. During treatment with various types of dialyzers further stimulation occurs, which, however, is highly dependent on the individuals under study and the material of the membranes used.

Only a few studies have addressed the question whether coagulation activity differs between HD and HDF. From a comparative analysis between high-flux HD and pre-dilution HDF it appeared that TAT and D-dimer generation at identical anti-Xa levels was considerably higher during HDF [21]. On the other hand, when the dose of the LMWH enoxaparin was kept constant and anti-Xa activity was compared between online postdilution HDF (substitution volume 18 L), low flux HD and high-flux HD, anticoagulant activity was significantly lower during HDF than during both high-flux HD and low-flux HD (low-flux HD: 0.71 ± 0.17, high-flux HD: 0.35 ± 0.17 and HDF: 0.19 ± 0.11 IU/ml, $p < 0.005$) [22]. UHep and LMWH dose-finding studies are described in the paragraph below.

Anti-coagulation During Hemodialysis and Hemodiafiltration

Unfractionated heparin (UHep) has been the standard anticoagulant in HD for decades [23]. It has both anti-Xa and anti-IIa activity and its presence can be estimated by the activated prothrombin time (aPTT). More recently, low molecular heparins (LMWH) have emerged as an alternative anticoagulant, because of a more simple mechanism of action (more powerful inhibition of the conversion of factor X to factor Xa without

an effect on thrombin, which reduces the bleeding risk in patients on this anticoagulant therapy), a more rapid onset of action, less platelet activation [24] and less fibrin deposition onto the dialyzer [25]. In addition, a single bolus injection at the start of HD is usually sufficient to obtain adequate anticoagulation during the entire duration of the dialysis session [26]. A detailed discussion of the merits and disadvantages of both types of anticoagulants in HD is beyond the scope of this chapter [27, 28].

Data comparing UHep and LMWH use in HDF are limited. From a study in patients who were treated with low-flux HD (n=28) and HDF (n=26), it appeared that both treatments induced adequate anticoagulation without major risk of bleeding [29]. Plasma anti-Xa activities were similar. Laboratory measurements in HDF patients indicated that aPTT and TAT (MW 90 kD) values were lower during treatment with the LMWH nadroparin (MW 1.7 kD), while plasma anti-Xa activity was higher. In addition, platelet-derived BTG (MW 36 kD) and PF4 (MW 358 kD) were lower after administration of LMWH. Other differences between HD and HDF were not described in this study.

From a dose-finding study in patients who underwent either high-flux HD (n=22) or online post-dilution HDF (n=33) it appeared that the optimal dalteparin (MW 6 kD) dose is approximately 60±10 IU/kg, the desirable target range of anti-Xa activity at 1 h 0.4–0.75 IU/ml and <0.4 IU/ml at the end of a session [30]. Differences in efficacy and side effects were not found between HD and HDF while accumulation did not occur in either modality. As dialysis time is an important determinant of end-dialysis anti-Xa activity, it was concluded that patients with a shorter dialysis time may need dosing in the lower range and individuals with longer dialysis time near the upper range. Comparable results were described with the synthetic LMWH fondaparinux (MW 1.7 kD) in five patients suffering from heparin-induced thrombocytopenia (HIT), who were treated with online postdilution HDF [31]. Despite its almost complete renal excretion and a terminal half-life of 17–20 h, accumulation did not occur during this type of treatment, most likely due to removal by convection. To obtain the desired anti-Xa activity both after 1 h (0.4–0.6 IU/ml) and at the end of the session (<0.4 IU/ml), 0.03 mg/kg appeared to be the optimal bolus at the start of HDF after a number of adjustments. At this dose no bleeding episodes were observed and only minor clotting occurred. Thrombocytopenia did not occur in 160 sessions.

Two large randomized, controlled trials, comparing HDF with HD, reported anticoagulant use during treatment with the two modalities. In the Turkish HDF Study the dose of UHep was approximately 25 % higher in HDF patients as compared to individuals who were treated with high-flux HD [32]. In CONTRAST [33], the dose of LMWH (mainly nadroparin and dalteparin) was approximately 10 % higher in the HDF group as compared to patients who were treated with low-flux HD [34]. As the MW of UHep is 5–30 kD and of LMWH 2–8 kD, removal by convection, as demonstrated for the LMWH enoxaparin during HD with high-flux membranes, [35] is a potential option for both substances. Of note, protein binding, which determines the free fraction available for elimination and bioavialability, differs considerably between the commercially available LMWHs, varying between 80 % for enoxaparin and <10 % for dalteparin [36]. For UHep protein binding is approximately 90 %. Other explanations for the requirement of high doses of anticoagulants during HDF include the elevated TMP and marked hemoconcentration.

Hemodiafiltration with Reduced Doses or No Anticoagulation in the Extra-Corporeal Circuit

As the administration of both UHep and LMWH has been related to unfavorable side effects, including platelet activation and hypertriglyceridemia, attempts have been made to reduce their doses. From a recent study in online postdilution HDF with a heparin-grafted polyacrylonitril (HeprAN) membrane, it appeared that the dose of the LMWH nadroparin (MW 1.7 kD) could be reduced by 60 % without noticeable clinical side-effects but with similar concentrations of TAT complexes, i.e. coagulation activation, as found during standard anticoagulation [37]. Other attempts to reduce or even avoid the use of UHep or LMWH during HDF include the application of pre-dilution HDF and regional citrate anticoagulation without [38] or with calcium-containing dialysate [39]. While especially the latter modality was characterized by a high incidence of clotting in the venous bubble trap, a study on pre-dilution HDF with reduced doses of the LMWH enoxaparin (MW 4.5 kD) was prematurely discontinued because of a significantly higher occurrence of major clotting incidents compared to standard regimes [40]. In CONTRAST, a small substudy was performed in patients with a temporarily contra-indication for systemic anticoagulation. Patients who were randomized to postdilution HDF were switched to the predilution mode and those randomized to HD were treated with regional citrate anticoagulation. A total of 14 patients (HDF 9; HD 5) underwent 29 treatments. Preliminary data indicate that 74 % of the HDF patients successfully completed the sessions compared to 90 % in the HD group.

Interestingly, the use of a citrate-based dialysate in online postdilution HDF appeared safe and allowed the exclusion of both the LMWH enoxaparin and UHep in most cases [41]. As ionized calcium diffuses from the blood into the dialysate and the calcium-citrate-complex from dialysate into the blood, ionized calcium decreased while total calcium remained unaltered, if compared to treatment with standard dialysate. The maximum plasma citrate concentration only slightly exceeded the upper limit of the normal range. In 120 sessions, side effects were not described.

Summary and Practical Advice

During the course of CKD, the hemostatic balance is disturbed due to alterations in the coagulation cascade, inhibitors of the coagulation system, the fibrinolytic pathway, platelets and endothelial cells. Hence, CKD is characterized by both a bleeding and a pro-thrombotic tendency.

During dialysis the blood of the patients is exposed to the foreign materials of the ECC, mechanical forces within the ECC and the anticoagulation administered during treatment. As a result, coagulation activation, as measured particularly by an increase in plasma TAT complexes and a decrease of individual clotting factors,

increases depending on the type of dialysis membrane used and individual patient characteristics. In addition, activation of platelets, as measured by an increase in the expression of the platelet surface marker CD62p and release of platelet granulation products, occurs. With the exception of the platelet degranulation product BTG, treatment-induced alterations in hemostatic parameters are more pronounced during HDF than HD, most probably due to a higher TMP and increased hemoconcentration.

Clinical studies revealed that anti-Xa activity is lower during HDF than during HD, at similar LMWH dosage. When anti-Xa was kept constant, higher doses of LMWH were necessary during treatment with HDF. In two randomized controlled trials comparing HDF with HD, post hoc analysis showed that both heparin and LMWH doses were higher in patients treated with HDF. Therefore, visible clotting of the dialyzer and air bubble trap, and pressure monitoring at the arterial line is of utmost importance. To avoid clot formation within the dialyzer and guarantee an undisrupted HDF procedure as much as possible, a higher loading dose may be advisable. When measuring anti-Xa activity, a concentration of 0.4–0.6 IU/ml after 1 h and 0.4 IU/ml at the end of the session appears sufficient. When using the LMWH fondaparinux, a dose of 0.3 mg/kg appeared the optimal bolus at the start of treatment while 60 IU/kg appears appropriate for dalteparin. In case of a contraindication for intravenous anticoagulation, use of pre-dilution HDF without administration of UHep or LMWH is an option, although published results are somewhat disappointing. Depending on the experience of the medical and technical staff, application of online post-dilution HDF with citrate-based dialysate may offer a suitable option.

Future studies are needed to assess first, whether the higher doses of UHep and LMWH during HDF are a reflection of the more bio-incompatible conditions within the dialyzer or result from removal by convection. Second, to assess whether higher doses of anticoagulants are correlated with clinical outcome (either favorable or adverse) or just an innocent bystander of HDF treatment.

Teaching Points

- Patients with chronic kidney disease (CKD) develop a variety of hemostatic disorders over time
- As a result, CKD patients suffer from both a bleeding tendency and a predisposition for clotting
- Abnormalities include the coagulation cascade, inhibitors of coagulation, fibrinolytic pathway, platelets and endothelial cells
- In hemodialysis (HD) patients, both the accumulation of uremic toxins and the bio-incompatibility of the extracorporeal circuit (ECC) play an important role in the hemostatic abnormalities
- Not only the dialyzer, but also other components of the ECC, intra-dialyzer hemoconcentration, mechanical forces and administration of intravenous anticoagulants contribute to this process

- Evaluation by electron microscopy revealed that platelets from a HD patient are smaller and hold less granule contents
- As both hemoconcentration and transmembrane pressure (TMP) are considerably increased in HDF, even further derangements occur in hemodiafiltration (HDF)
- Both in Turkish HDF Study and CONvective TRAnsport Study, higher doses of anticoagulants were administered to HDF patients
- Since middle molecular weight uremic toxins, such as platelet-derived beta-thromboglobulin, are removed during HDF, it is unclear whether the more bio-incompatible conditions within the ECC during HDF are harmful or not

References

1. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Hemost. 2004;30(5):579–89.
2. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost. 2010;36(1):34–40.
3. Molino D, De LD, De Gaspare SN. Coagulation disorders in uremia. Semin Nephrol. 2006;26(1):46–51.
4. Gritters-van den Oever M, Grooteman MP, Bartels PC, Blankestijn PJ, Bots ML, van den Dorpel MA, et al. Post-dilution haemodiafiltration and low-flux haemodialysis have dissimilar effects on platelets: a side study of CONTRAST. Nephrol Dial Transplant. 2009;24(11):3461–8.
5. Schmitt GW, Moake JL, Rudy CK, Vicks SL, Hamburger RJ. Alterations in hemostatic parameters during hemodialysis with dialyzers of different membrane composition and flow design. Platelet activation and factor VIII-related von Willebrand factor during hemodialysis. Am J Med. 1987;83(3):411–8.
6. Schoorl M, Schoorl M, Bartels PC. Changes in platelet volume, morphology and RNA content in subjects treated with haemodialysis. Scand J Clin Lab Invest. 2008;68(4):335–42.
7. Gritters M, Borgdorff P, Grooteman MP, Schoorl M, Schoorl M, Bartels PC, et al. Platelet activation in clinical haemodialysis: LMWH as a major contributor to bio-incompatibility? Nephrol Dial Transplant. 2008;23(9):2911–7.
8. Schoorl M, Bartels PC, Gritters M, Fluitsma D, Musters R, Nube MJ. Electron microscopic observation in case of platelet activation in a chronic haemodialysis subject. Hematol Rep. 2011;3(2):e15.
9. Gritters M, Grooteman MP, Schoorl M, Schoorl M, Bartels PC, Scheffer PG, et al. Citrate anticoagulation abolishes degranulation of polymorphonuclear cells and platelets and reduces oxidative stress during haemodialysis. Nephrol Dial Transplant. 2006;21(1):153–9.
10. Myrup B, Yokoyama H, Kristiansen OP, Ostergaard PB, Olivecrona T. Release of endothelium-associated proteins into blood by injection of heparin in normal subjects and in patients with Type 1 diabetes. Diabet Med. 2004;21(10):1135–40.
11. den Gritters-van OM, Schoorl M, Schoorl M, Bartels PC, Grooteman MP, Nube MJ. The role of the extracorporeal circuit in the trapping and degranulation of platelets. Blood Purif. 2009;28(3):253–9.
12. Sirolli V, Ballone E, Di Stante S, Amoroso L, Bonomini M. Cell activation and cellular-cellular interactions during hemodialysis: effect of dialyzer membrane. Int J Artif Organs. 2002; 25(6):529–37.
13. Libby P, Geng YJ, Aikawa M, Schoenbeck U, Mach F, Clinton SK, et al. Macrophages and atherosclerotic plaque stability. Curr Opin Lipidol. 1996;7(5):330–5.

14. Miljic P, Miljic D, Cain JW, Korbonits M, Popovic V. Pathogenesis of vascular complications in Cushing's syndrome. Hormones (Athens). 2012;11(1):21–30.
15. Adams MJ, Irish AB, Watts GF, Oostryck R, Dogra GK. Hypercoagulability in chronic kidney disease is associated with coagulation activation but not endothelial function. Thromb Res. 2008;123(2):374–80.
16. Sabovic M, Salobir B, Preloznik ZI, Bratina P, Bojec V, Buturovic PJ. The influence of the haemodialysis procedure on platelets, coagulation and fibrinolysis. Pathophysiol Haemost Thromb. 2005;34(6):274–8.
17. Preloznik ZI, Sabovic M, Salobir B, Buturovic PJ. Characterization of the pro-thrombotic state in CAPD patients. Ren Fail. 2008;30(6):597–602.
18. Bartels PC, Schoorl M, Schoorl M, Wiering JG, Nube MJ. Activation of coagulation during treatment with haemodialysis. Scand J Clin Lab Invest. 2000;60(4):283–90.
19. Bartels PC, Schoorl M, Schoorl M, Nube MJ. Deviations in coagulation activation due to treatment with different haemodialysis membranes. Scand J Clin Lab Invest. 2003;63(6):417–24.
20. Ishii Y, Yano S, Kanai H, Maezawa A, Tsuchida A, Wakamatsu R, et al. Evaluation of blood coagulation-fibrinolysis system in patients receiving chronic hemodialysis. Nephron. 1996;73(3): 407–12.
21. Klingel R, Schaefer M, Schwarting A, Himmelsbach F, Altes U, Uhlenbusch-Korwer I, et al. Comparative analysis of procoagulatory activity of haemodialysis, haemofiltration and haemodiafiltration with a polysulfone membrane (APS) and with different modes of enoxaparin anticoagulation. Nephrol Dial Transplant. 2004;19(1):164–70.
22. Sombolos KI, Fragia TK, Gionanlis LC, Veneti PE, Bamichas GI, Fragidis SK, et al. The anticoagulant activity of enoxaparin sodium during on-line hemodiafiltration and conventional hemodialysis. Hemodial Int. 2009;13(1):43–7.
23. Cronin RE, Reilly RF. Unfractionated heparin for hemodialysis: still the best option. Semin Dial. 2010;23(5):510–5.
24. Aggarwal A, Whitaker DA, Rimmer JM, Solomon RJ, Gennari FJ, Sobel BE, et al. Attenuation of platelet reactivity by enoxaparin compared with unfractionated heparin in patients undergoing haemodialysis. Nephrol Dial Transplant. 2004;19(6):1559–63.
25. Hofbauer R, Moser D, Frass M, Oberbauer R, Kaye AD, Wagner O, et al. Effect of anticoagulation on blood membrane interactions during hemodialysis. Kidney Int. 1999;56(4):1578–83.
26. Sagedal S, Hartmann A, Sundstrom K, Bjornsen S, Fauchald P, Brosstad F. A single dose of dalteparin effectively prevents clotting during haemodialysis. Nephrol Dial Transplant. 1999;14(8):1943–7.
27. Davenport A. Review article: low-molecular-weight heparin as an alternative anticoagulant to unfractionated heparin for routine outpatient haemodialysis treatments. Nephrology (Carlton). 2009;14(5):455–61.
28. Davenport A. Optimization of heparin anticoagulation for hemodialysis. Hemodial Int. 2011;15 Suppl 1:S43–8.
29. Stefoni S, Cianciolo G, Donati G, Coli L, La MG, Raimondi C, et al. Standard heparin versus low-molecular-weight heparin. A medium-term comparison in hemodialysis. Nephron. 2002;92(3):589–600.
30. Sridharan S, Berdeprado J, Sivalingam M, Farrington K. Dalteparin dosing in high-flux haemodialysis and haemodiafiltration. Nephron Clin Pract. 2012;122(1–2):53–7.
31. Mahieu E, Claes K, Jacquemin M, Evenepoel P, De Op BK, Bogaert AM, et al. Anticoagulation with fondaparinux for hemodiafiltration in patients with heparin-induced thrombocytopenia: dose-finding study and safety evaluation. Artif Organs. 2013;37(5):482–7.
32. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF study. Nephrol Dial Transplant. 2013;28(1):192–202.
33. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.

34. de Roij van Zuijdewijn C, Nube MJ, Blankestijn PJ, ter Wee PM, van den Dorpel MA, Bots ML, et al. The prescribed dose of low molecular weight heparin increases after assigning patients to hemodiafiltration (HDF) treatment. J Am Soc Nephrol 2014;25 (abstract edition): 292A.
35. McMahon LP, Chester K, Walker RG. Effects of different dialysis membranes on serum concentrations of epoetin alfa, darbepoetin alfa, enoxaparin, and iron sucrose during dialysis. Am J Kidney Dis. 2004;44(3):509–16.
36. Green D, Hirsh J, Heit J, Prins M, Davidson B, Lensing AW. Low molecular weight heparin: a critical analysis of clinical trials. Pharmacol Rev. 1994;46(1):89–109.
37. Frasca GM, Sagripanti S, D'Arezzo M, Oliva S, Francioso A, Mosconi G, et al. Post-dilution hemodiafiltration with a heparin-grafted polyacrylonitril membrane. Ther Apher Dial. 2015;19(2):154–61.
38. Kovac J, Gubensek J, Pernat AM, Buturovic-Ponikvar J, Kersnic B, Pretnar J, et al. Citrate anticoagulation during post-dilution hemodiafiltration with a high cut-off (Theralite) membrane. Ther Apher Dial. 2011;15(3):283–6.
39. Buturovic-Ponikvar J, Cerne S, Gubensek J, Ponikvar R. Regional citrate anticoagulation for hemodialysis: calcium-free vs. calcium containing dialysate – a randomized trial. Int J Artif Organs. 2008;31(5):418–24.
40. Hamzi MA, Hassani K, Alayoud A, Arache W, Bahadi A, Kasouati J, et al. Predilution online hemodiafiltration: which dose of anticoagulation? Nephrol Ther. 2013;9(1):21–5.
41. Aniort J, Petitclerc T, Creput C. Safe use of citric acid-based dialysate and heparin removal in postdilution online hemodiafiltration. Blood Purif. 2012;34(3–4):336–43.

Part IV
Clinical Aspects of Hemodiafiltration

Chapter 16
Clinical Trials on Hemodiafiltration

Muriel P.C. Grooteman, Menso J. Nubé, and Michiel L. Bots

Abstract In the present chapter, several clinical hemodiafiltration (HDF) studies are discussed, with special emphasis on the reliability of the methodology used. These studies differ widely in design, end points, patient numbers, treatment and comparator groups, and amount of convection volume in the treatment arms. Recently, three large randomized controlled trials (RCT) have been performed comparing survival between online postdilution HDF and hemodialysis (HD). While neither CONTRAST nor the Turkish HDF study showed differences between study arms, in the Spanish ESHOL study the mortality risk was significantly lower in HDF patients (HR 0.70; 95 % CI 0.53–0.92). In all three studies, post-hoc (on-treatment) analysis showed a survival benefit up to 40 % for patients treated with high-volume HDF (convection volume >20–22 L/treatment). Apart from these RCTs, in the last 4 years five meta-analyses on convective therapies have been performed, including four on aggregated study results and one on pooled individual patient data (IPD). Since in the latter approach all individual patient data from trials are ascertained, put together and combined to a new data base, this type of meta-analysis is most reliable for making adjustments and evaluating subgroup results. Notably, in both types of meta-analyses the hazard ratio (HR) for mortality of online HDF (as compared to HD) was about 0.83–0.86, indicating a 15 % lower mortality risk for patients treated with HDF. From the IPD meta-analysis it appeared that the mortality risk was even lower when high convection volumes are applied (HR 0.78; 95 % CI 0.62–0.98). Finally, meta-analysis on modern convective therapies should include only online treatments with a convection volume >20 L/session.

Keywords Randomized controlled trials • Observational analysis • Cohort • Bias • Meta-analysis • Survival • Mortality risk • Methodology • Individual patient data meta-analysis

M.P.C. Grooteman, MD, PhD (✉) • M.J. Nubé, MD, PhD
Department of Nephrology, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081HV, The Netherlands
e-mail: mpc.grooteman@vumc.nl; mensonube@gmail.com

M.L. Bots
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_16

Introduction: Hemodiafiltration Trials

Since the start of hemodiafiltration (HDF) in the seventies of the twentieth century [1], many reports have been published on the clinical effects of convective techniques. These studies, however, vary considerably with respect to the techniques compared (e.g. off-line HDF, pre-and post-dilution online HDF, acetate free biofiltration [AFB], hemofiltration [HF]), the treatment modality in the reference arms (low or high-flux hemodialysis [HD]), the achieved convection volume in the treatment arm, their design (observational studies, intervention studies and meta-analyses of randomized clinical trials [RCTs]), the diverse end points (ranging from the effect on single solutes or cytokines to fatal and non-fatal disease) and patient numbers (from less than 50 to several thousands).

This chapter will focus on the results of RCTs with clinical endpoints on online post-dilution HDF. First, however, we will discuss the results of large observational studies which were conducted before the publication of these RCTs. Thereafter, a number of systematic reviews and meta-analysis on convective therapies will be described, that have been published in the past 10 years. Meanwhile, a variety of methodological issues important for the interpretation of the findings from the various studies will be addressed.

Observational (Cohort) Studies on Hemodiafiltration and Clinical Endpoints

In Europe, several cohorts of patients were studied in order to compare the treatment effects of HD with HDF in the last decades.

In 1999, an observational Italian study was published, including 6444 patients with end stage kidney disease [2]. Of these, 188 started on HDF or HF, whereas 6256 started treatment with HD. During the study, therapy was changed in several patients, mainly to HDF (n = 894). Treatment was analyzed as a time dependent covariate. No differences in mortality were observed (RR H(D)F compared to HD: 0.90, 95 % CI 0.76–1.06). The main finding reported by the authors was that the risk of dialysis related amyloidosis decreased in patients treated with convective techniques (risk of surgery for carpal tunnel syndrome H(D)F: RR 0.59, 95 % CI 0.36–0.96, p = 0.034).

In 2006, the results of treatment with online HDF in patients in the European Clinical Database (EuCliD) were presented in a letter [3], precluding critical appraisal of the study. In this observational study encompassing 2564 patients, followed for 12 months, an odds ratio for all-cause mortality of 0.57 (95 % CI 0.38–0.87, and an odds ratio after adjustment OR 0.65 [95 % CI 0.42–0.99]) was observed in patients treated with online HDF (n = 394) compared to HD. The convection volume was not reported.

The DOPPS data were reported in 2006 by Canaud et al. [4]. In this prospective, non-randomized observational study, 2165 patients were followed between 1998 and 2001 in five European countries. Four different treatment modalities were compared: low-flux HD (n = 1366), high-flux HD (n = 546), low-efficiency HDF (n = 156, substitution volume 5–14.9 L/treatment), and so-called high-efficiency HDF (n = 97, substitution volume 15–24.9 L/treatment). Treatment with high-efficiency HDF was associated with a relative risk reduction of mortality of 35 % (p = 0.01), as compared to low-flux hemodialysis, a finding which remained after extensive adjustments.

In Italy, a prospective observational study was performed in 757 patients (the RISCAVID study) which was published in 2008 [5]. Treatment with low- or high-flux HD (n = 424) was compared to treatment with HDF with bags (n = 130: AFB, n = 74: HDF, convection volume 10–15 L/treatment) and online HDF (n = 129, convection volume 22–25 L/session). After a follow up of 30 months, treatment with HDF (either online or with bags) was associated with a reduced risk of all-cause mortality, after adjustment (RR 0.78, p = 0.01).

In the United Kingdom, the results of an observational study in 858 incident patients were reported in 2009 [6]. Patients were treated predominantly with online HDF (n = 232). In this group, 79 % of treatments were delivered as HDF, with a mean filtration volume of 14.9 L/treatment (range 5.8–33.2 L). The comparator group was treated exclusively with high-flux HD (n = 626). The mortality risk was significantly reduced in patients treated predominantly treated with HDF (HR 0.45; 95 % CI 0.35–0.59, p < 0.001), after adjustment for age, gender, BMI and comorbidity.

Quite recently, several observational analyses were derived from the EuClid Database [7–10]. In Romania, 221 prevalent patients treated with online HDF (mean convection volume 22.2 L) were matched with a propensity score (PS) to 431 patients treated with HD [8]. Online HDF was associated with a reduced mortality risk (HR 0.62; 95 % CI 0.42–0.93). As before matching both patients groups differed markedly (due to the indication for HDF as formulated in the Romanian law), unmeasured confounding might play a considerable role. For incident patients, the mortality risk was lower as well (PS score matched groups, 265 patients on HDF, 530 HD patients, HR 0.22; 95 % CI 0.11–0.43).

A study on 442 incident patients in three other Balkan countries failed to show a significant effect on mortality risk in high-volume HDF (substitution volume 23.3 L/treatment) as compared to high-flux HD, in a time dependent analysis (HR 0.48; 95 % CI 0.20–1.16) [7]. In this study, somewhat healthier patients were treated with HDF and 44 % changed treatment modality during follow up.

From the same database, data were used from NephroCare centers in 12 European countries and 2 propensity score matched groups of 795 incident patients were formed. Patients were followed for 2.0 years (HD group) or 1.6 years (high-volume HDF group) [9]. About 20 % of patients were lost to follow up in both groups and a large number of modality switches occurred. In this study, a non-significant survival advantage of HDF was found (HR 0.88; 95 % CI 0.67–1.15).

Finally, the optimal convection volume was evaluated in a retrospective analysis on 2293 incident HDF patients from the EuClid database [10]. After correction for several confounders, the survival benefit started at a weekly convection volume of >55 L (i.e. 18.3 L/treatment) and reached a plateau at 75 L/week (25 L/treatment).

Some Methodological Issues Regarding Cohort Studies in Evaluation Treatment Efficacy

Generally, the estimate of a treatment effect from cohort studies is regarded less reliable than from RCTs. In studies comparing the effect of treatment on a specific end point (e.g. reduction in mortality), one is interested in the treatment effect only. However, the risk of death in the hemodiafiltration study arm that is observed is a summation of the treatment effect, the natural history of the patient group, bias due to observers, changes in the patient group that affect the risk of death and effects of loss to follow-up. The same accounts for the risk of death in the hemodialysis group. Therefore, these factors should be controlled for when evaluating the treatment effects in cohort studies. Adjustment for baseline factors that are related to the treatment and to the risk of the outcome is mandatory. Observer bias should be minimized by choosing an outcome measurement that cannot be biased by observers, e.g. death. Changes in patient group, e.g. behavior and lifestyle of patients or treatments may be adequately addressed by using adjustments for those variables that change over time, e.g. salt intake, weight loss, occurrence of non-fatal disease (pneumonia, fractures), or transplantation (time varying co-variables). When the risk of receiving a kidney transplantation is related to the treatment and the transplantation is related to the risk of the outcome, relations are biased. Finally, loss of follow-up should be evaluated, in order to check whether it differs across treatment arms and whether it relates to the risk of death. For example, when during the conduct of a study, half of the patients withdrew because they knew they would not survive the next 6 months, the risk of death in that study would be severely underestimated, and thus the result is biased. As these aspects are not always clearly addressed in cohort studies, the reported estimates may be biased to a varying extent.

Randomized Controlled Trials on Hemodiafiltration, Other Clinical End Points

Many randomized or cross-over trials on clinical end points other than mortality have been performed. Here, we discuss some of the larger trials briefly.

In 1996, Locatelli et al. published the results of a RCT in which 380 patients were included. Patients were randomized to four groups: HD with cuprophane membranes (n = 132), low-flux HD with polysulfone membranes (n = 147), high-flux HD with polysulfone membranes (n = 51) or post-dilution HDF with a convection volume of 8–12 L/session (n = 50) [11]. During the study, which lasted 24 months, 228 patients were lost to follow up for other reasons than death (among which 139 for

'technical reasons'). Loss to follow-up does not necessarily bias the results. This only occurs when loss to follow-up is differential, i.e. related to both treatment and risk of death. An example of the latter is when patients receive a kidney transplant. Since these individuals leave the study alive, and are censored (i.e., no longer followed for death) they are no longer at risk to die in a study context. When loss to follow-up is non-differential (random), the consequence is only loss of precision, i.e. large confidence intervals, whereas a true relative risk is reported. In the present study, no differences were found in the two primary end points: hypotensive episodes and nutritional status, whereas mortality was similar in the four groups.

In 2000, two relatively small RCTs were published, in which 44–50 patients were randomized between low-flux HD or HDF. These trials were too small to draw conclusions on clinical end points [12, 13].

In a recent Italian study, the effect of several techniques on intradialytic hypotension was investigated in 146 patients randomized to low-flux HD (n = 70), online pre-dilution HF (n = 36, median substitution volume 60.4 L/session) and online pre-dilution HDF (n = 40, median substitution volume 39.9 L/session) [14]. Patients with residual diuresis of >200 ml/day were excluded. After a median follow up of 1.5 year, a risk reduction of 31–54 % for intradialytic symptomatic hypotension was observed for the convective treatments (online pre-dilution HDF: OR 0.46, 95 % CI 0.33–0.63). Of note, this large effect might have been overestimated, since it was unclear how the repeated correlated nature of the data (hypotensive episodes occurring more than once in a single patient) was taken into account in the statistical analysis.

Tessitore et al. compared AFB, a form of HDF with bags (off-line, convection volume about 10 L/treatment) with low- or high-flux HDs in a randomized controlled trial in 371 patients [15]. During the study, about 20 % of patients were lost to follow-up in both treatment arms. After 36 months, treatment with AFB resulted in a significant reduction in the number of intradialytic hypotensive episodes. Cardiovascular mortality was comparable in the two treatment groups, although this trial was not designed to assess such an effect.

Thus, from these studies it appears that the incidence of intradialytic hypotension is reduced in patients treated with convective techniques. For further reading see Chaps. 17 and 19.

Finally, over the past decades there have been several (cross-over) trials that addressed the effects of online HDF on alternative outcomes, such as left ventricular mass, anemia, quality of life, hemoglobin, beta-2 microglobulin and other laboratory measurements. These items are discussed in other chapters.

Randomized Controlled Trials on Online Post-Dilution Hemodiafiltration Designed for Mortality as Primary End-Point

In this paragraph, the results of three large RCTs, comparing HDF with HD and primarily designed to assess hard clinical outcomes, will be discussed in order of publication date. The results of some other studies are pending [16].

The Dutch CONvective TRAnsport STudy (CONTRAST)

The CONTRAST study (NCT 00205556) was performed in 29 centers in the Netherlands (n = 26), Canada (n = 2) and Norway (n = 1) [17]. Seven hundred fourteen patients were randomized between 2004 and 2009 between treatment with low-flux HD and online post-dilution HDF, both with ultrapure dialysate. Main exclusion criteria were treatment with high-flux HD or H(D)F in the preceding 6 months, severe non-adherence regarding the dialysis treatment and a life-expectancy of <3 months due to non-renal disease. Neither vascular access, nor residual renal function was considered an exclusion criterion.

The primary endpoint was all cause mortality, and the main secondary endpoint was a composite of fatal and non-fatal cardiovascular events. Of 358 HDF patients, 121 discontinued treatment during the study due to transplantation, switch to another center or therapy, or other reasons. Of 356 HD patients, 118 patients discontinued the allocated treatment. Importantly, despite discontinuation of the allocated treatment, all patients (100 %) were followed until the end of the study in 2010 or death, whichever occurred first.

Mean follow up was 36 months (range 5–79); during this period 269 deaths occurred in 2170 person-years. The incidence of all-cause mortality was not affected by treatment assignment (HR 0.95; 95 % CI 0.75–1.20), as was the incidence of the composite end point of fatal and non-fatal cardiovascular events (HR 1.07; 95 % CI 0.83–1.39). In pre-specified subgroup analysis, clinical outcome was not related to residual kidney function, diabetes, low serum albumin or a high dialysis vintage. While the target convection volume was set at 24 L/treatment, the mean achieved volume was only 20.7 L/treatment. Post hoc analysis showed a significantly lower mortality in the group of patients treated with a high convection volume: >21.95 L/treatment (highest tertile) was associated with a 39 % lower mortality as compared to HD (HR 0.61; 95 % CI 0.38–0.98), which remained after extensive adjustment for determinants of mortality and convection volume.

The Turkish Hemodiafiltration Study

The Turkish HDF study (NCT00411177) was conducted between 2007 and 2010 in 10 centers, including 782 patients, randomized between online post-dilution HDF and high-flux HD [18]. Patients with central venous catheters were excluded, as were patients with blood flow <250 ml/min and/or residual urine output of >250 ml/day.

The primary end point was a composite of all-cause mortality and first non-fatal cardiovascular event. Of 391 patients treated with HDF, 110 discontinued the study (28 %), including 40 (10 %) who terminated early due to vascular access problems, resulting in insufficient blood flow rate. Of 391 patients randomized to HD, 90 patients (23 %) dropped out (none due to vascular access problems). Importantly, these patients were censored alive at the moment they discontinued the treatment

and not followed for the primary outcome after discontinuation. Hence, when the reasons for discontinuation are related to the treatment modality and to the risk of the primary outcome, the main treatment effect may be biased. Mean follow up was 23 months (range 1–38) and the HR of HDF for the composite of mortality and first cardiovascular event was 0.82 (95 % CI 0.59–1.16), for all-cause mortality 0.79 (95 % CI 0.55–1.14) and for cardiovascular mortality 0.72 (95 % CI 0.45–1.13).

The mean substitution volume in the HDF group was 17.2 L/treatment. As the mean intradialytic weight gain was 2.4 L per treatment (3.5 % of body weight, mean post dialysis body weight in the HDF group 68.1 kg), the average convection volume was 19.6 L/treatment. From a post-hoc analysis it appeared that patients who achieved a convection volume above the median showed a lower mortality risk than patients with a convection volume below the median (HR 0.54; 95 % CI 0.33–0.88). These association remained after extensive adjustments for age, gender, diabetes, cardiovascular disease, dialysis vintage, vascular access, interdialytic weight gain, blood flow rate, hemoglobin, albumin, phosphate and eKt/V (HR 0.54; 95 % CI 0.31–0.93).

The Catalonian Hemodiafiltration Study (ESHOL)

The ESHOL study (NCT00694031) included 906 Spanish dialysis patients in 27 units, who were randomized between online post-dilution HDF (n = 456) and HD (n = 450) [19]. In the HD group, 8 % of the patients was treated with low-flux and 92 % with high-flux membranes. Patients with a temporary non-tunneled venous catheter were excluded, as well as patients on immunosuppressive therapy. After randomization, patients not achieving >18 L of convection volume, or not receiving the allocated treatment for >2 months were withdrawn from the study (information on number of patients withdrawn was not provided). No information was collected on residual kidney function.

Mean follow up was 23 months. Three hundred fifty five patients prematurely completed the study and were censored alive, being 36 % of participants in the HD group and 42 % in the HDF group. As described earlier, this may have introduced an information bias (overestimation of the treatment effect) in the main estimate, if premature discontinuation of the study was related to the treatment modality (HDF) and to the risk of death. In patients treated with HDF, the median convective volume achieved was 22.9–23.9 L/treatment. Two hundred seven events were observed in 1730 patient-years. A significant 30 % risk reduction in mortality was observed in the HDF group (HR 0.70; 95 % CI 0.53–0.92), while the HR for cardiovascular mortality was 0.67 (95 % CI 0.44–1.02). Similarly, as in CONTRAST and the Turkish HDF study, in a post hoc analysis, a higher achieved convection volume was associated with a lower mortality risk (HR highest tertile, i.e. >25.4 L/treatment 0.55; 95 % CI 0.34–0.84), if compared to HD patients.

Reflection on Individual RCTs

The three RCTs primarily designed for assessing an effect of online HDF on mortality showed different results. In general there is a number of issues one has to address in order to explain such findings assuming the studies were sufficiently powered for the primary outcome: (1) differences are due to biases that are differently operating across the studies; (2) differences are due to differences in treatment intensity (dosage) across studies; (3) differences are due to chance; (4) differences are due to differences in participants across studies.

Bias

As all three RCTs were well balanced in baseline characteristics, the natural history of the disease (i.e., risk of death) in both treatment modality groups was comparable at the start of the study. In addition, since follow-up measurements were equal between treatment modalities in each of the study, no bias is expected in this respect. All trials had all-cause mortality as primary or secondary outcome, which is an unbiased outcome. Causes of death were generally assessed by an event committee blinded to allocation of treatment modality. Notably, the three RCTs did differ in their approach of censoring alive. Only in CONTRAST all patients were followed for death, irrespective of what happened during the trial (e.g. transplantation, or switch to another modality), whereas in the other trials this did not happen (individuals were censored alive). In fact, the other RCTs reported results from an 'on treatment' analysis. In CONTRAST the 'on treatment' analyses yielded similar results as the other three trials (HR around 0.82).

Treatment Intensity

The three RCTs clearly differed with respect to the average dose of convective volume that was delivered. Assuming that the convective volume is indeed important, this difference might explain the different trial results. However, informative bias, as described above, cannot be ruled out as an explanation for the different results. A clue that differences in the magnitude of the achieved convection volume across studies may indeed be the explanation for the dissimilar clinical outcome may come from the observation that the convective volume analyses were comparable, despite differences in informative bias across studies.

Differences in Patients

In order to have the differences in patient characteristics explain the differences in trial results, one should compare whether death rates differ across trials, and, from a pathophysiological point of view explain why effects of treatment differ by risk of

death. In all three RCTs, prevalent patients were studied. In ESHOL and CONTRAST mean age was about 65 years, dialysis vintage about 2–3 years, and 24–25 % of the patients suffered from diabetes mellitus. In Contrast, 44 % of patients had previous cardiovascular disease and 53 % residual diuresis; for ESHOL these data are not available. Death rates were 12 deaths/100 patient years in both trials. In the Turkish HDF study, however, patients were markedly younger (mean age 56 years), had a longer dialysis vintage (almost 5 years), and suffered more often from diabetes (34.7 %). No patients with residual diuresis were included, and 26.4 % had a history of cardiovascular disease. Death rates were lower than in the other two trials: 8 deaths/100 patient years. As of yet, no subgroups are identified in which HDF is of more benefit. Hence, although some differences in patients characteristics between the trials were observed, they do not directly seem to explain the different results.

Chance Finding

A RCT can be viewed as "just a measurement of a therapy effect" and as such, differences may indeed be just a chance finding as studies may falsely or correctly provide the good answer to the research question.

Meta-analyses of Convective Therapies

Generally it should be realized that when individual studies are biased, a meta-analysis is no more than the pooling of biased results. Only when adjustment for the biases that occurred in the studies involved can be performed, the truth will come closer. In addition, there are two types of meta-analyses to distinguish: the first is pooling aggregated results from publications, the second is one that collects all the individual participant data (IPD) from all trials and have the analysis rerun. The IPD meta analyses are best for making adjustments and evaluating subgroup results. This paragraph deals with the first approach.

In recent years, several meta-analyses on convective therapies have been published, see Table 16.1. The first was a Cochrane analysis in 2005 [20], that included 20 trials with 657 patients (8 cross over studies and 12 parallel arm studies). Mortality data were available from only 4 trials with 336 patients, depended heavily on the results of one single trial (with 205 patients) and suggested no difference in mortality risk for patients treated with HDF (after correction of an error: RR 1.68; 95 % CI 0.23–12.13) [21]. The authors concluded no treatment modality could be preferred over another because of inadequate power of the studies, which were of insufficient quality. Obviously, none of the recent RCTs could be included in this analysis.

Eight years later, a meta-analysis was published by Susantitaphong, comparing 'convective therapies' with low-flux HD [22]. Remarkably, 'convective therapies' included not only HF, HDF, and AFB but also high-flux HD. Hence, a therapy with virtually no convection (low-flux HD) was compared to therapies with a large range

Table 16.1 Overview of meta-analyses on convective therapies

1st author and year of publication	Convective therapy	Comparator	No of RCTs[a]	No of patients[a]	Effect on all-cause mortality	Effect on cardiovascular mortality
					RR (95 % CI)	RR (95 % CI)
Rabindranath (2005) [20]	HF, HDF, AFB	lfHD, hf HD	4	326 (–)	1.68 (0.23–12.13)	–
Susantitaphong (2013) [22]	HF, HDF, AFB, hfHD	lfHD	21 (3)[b]	4766 (3207)	0.88 (0.76–1.02)	0.84 (0.71–0.98)
Mostovaya (2014) [23]	HDF	lfHD, hf HD	6[c] (3)	2885 (2402)	0.84 (0.73–0.96)	0.73 (0.57–0.92)
Nistor (2014) [24]	HF, HDF, AFB	lfHD, hf HD	11 (6)	3396 (2889)	0.87 (0.70–1.07)[d]	0.75 (0.58–0.97)
Wang (2014) [26]	HF, HDF, AFB	lfHD, hf HD	10 (4)	2998 (2487)	0.83 (0.65–1.05)	0.85 (0.66–1.10)

RCT randomized controlled trial, *RR* relative risk, *CI* confidence interval, *HF* hemofiltration, *HDF* hemodiafiltration, *AFB* acetate free biofiltration, *hfHD* high-flux hemodialysis, *lfHD* low-flux hemodialysis

[a]Number of trials (resp patients) used for meta-analysis effect on all-cause mortality or (between brackets) cardiovascular mortality,

[b]For the Susantitaphong meta-analysis: number of convective study arms

[c]Only parallel arm RCTs (others: both cross-over and parallel arm RCTs)

[d]If studies with low convection volumes (<12 L/treatment) are excluded from this meta-analysis, the RR for mortality is 0.82 (95 % CI 0.72–0.93) [25]

of convection volumes. This meta-analysis based on aggregated data included 12,182 patients; mortality data were available for 4766 patients. In the 'convective' arm, more than 50 % of patients were treated with high-flux HD. The relative risk of mortality was 0.84 (95 % CI 0.71–0.98) for patients in the 'convective' arm as compared to low-flux HD. At the time of this meta-analysis, only one of the three recent RCTs on online HDF was included [17].

Mostavaya et al. compared exclusively HDF to (both low- and high-flux) HD in 2014 [23], including 2402 patients. The HDF arm consisted of both online post-dilution HDF (n = 1205, achieved convection volume in post-dilution >19 L/treatment) [17–19]; online mid-dilution HDF (n = 23, target convection volume 60 L/treatment, achieved volume not reported) [13]; offline HDF (n = 50, target convection volume 8–12 L/treatment) [11] or online pre-dilution HDF (n = 40, reinfusion volume 39.9 L/treatment) [14]. The RR for all-cause mortality with HDF was 0.84 (95 % CI 0.73–0.96), as compared to low- and high-flux HD.

In 2014 Nistor and colleagues compared (low- and high-flux) HD to convective techniques, including HF, offline HDF (with bags, including AFB) and online HDF [24]. Effects on mortality was estimated for 3396 patients. Of 1648 patients treated with convective techniques, 14 % (n = 227) were treated with low volume HDF (including AFB; convection volume ca 10 L/treatment) [11, 15]. The authors concluded that 'in low-quality evidence, convective therapies had little or no effect on all-cause mortality'. However, the RR for mortality was 0.87, indicating a 13 % lower mortality risk, with a corresponding p value of 0.10. Furthermore, after

removing studies with low-convection volume therapies from this analysis, the RR for mortality was 0.82 (95 % CI 0.72–0.93), suggesting a 18 % and significantly lower mortality risk [25]. The 'low-quality' of the evidence is partly due to the lack of treatment concealment, which is unrealistic in trials on dialysis therapies. It is up to the clinician to decide whether this is not only a statistically significant but also a clinically relevant effect.

Wang et al. reported in 2014 the results from a systematic review and meta-analysis, and compared 3220 patients treated with HDF or HF with low- and high-flux HD as comparator therapy in 16 trials [26]. The mortality data (2998 patients) showed a relative risk of 0.83 (95 % CI 0.65–1.05). In this analysis, one low-volume HDF study was included with 205 patients and 13 events [11].

Reflection on Recent Meta-analyses

As nicely pointed out by others, the results of a systematic review and meta-analysis depend on several factors, such as defining the research question, the literature search, the selection of trials to be included, and the choice of outcome measures [27]. Among these, the definition of 'convective therapy' seems of utmost importance. Strictly spoken, even high-flux HD is a convective therapy, as convection occurs due to internal filtration and net ultrafiltration. Although the exact convection volume in high-flux HD cannot be measured, it is estimated to be about 10 L/treatment [28]. The convection volume in the other therapies varied between 10 L/session in AFB [15] or offline HDF [11] and 22.9–23.9 L/session in the Spanish HDF study [19]. In modern convective therapies, high convection volumes are easily achievable. Hence, a relevant systematic review and meta-analysis should exclude low-convection volume treatments, such as high-flux HD, offline H(D)F and AFB, from the intervention arm. Only then, a proper statement can be made on the effect of modern (i.e. online) convective therapies.

Individual Participant Data Meta-analysis

The HDF pooling initiative has recently started. This project is an ongoing individual participant data (IPD) meta-analysis using data from large multicenter RCTs that compared the effects of online post-dilution HDF with standard HD on mortality in adult patients. At present, data have been collected from four large RCTs on this issue: CONTRAST, the ESHOL study, the Turkish HDF study and the French HDF study [16–19]. In the published papers, mortality follow-up data were complete for CONTRAST [17], but incomplete for 355 (39 %) of patients in the ESHOL study [19], and for 199 (25 %) patients in the Turkish HDF study [18], as patients were censored alive at the time they discontinued the randomized treatment. In the pooling project, additional follow-up data were collected and obtained for 352 of the 355

(99 %) ESHOL patients, and 148 of the 199 (74 %) Turkish study patients who had been censored alive. For the French study, data were complete for 95 % of patients. With these data, hazard ratios (HRs) and 95 % confidence intervals (95 % CI) comparing the effect of online HDF versus HD on all-cause and cause-specific mortality were calculated using Cox proportional hazard regression models. After a median follow-up of 2.5 years (IQR 1.9–3.0), 769 of the 2793 participants had died (among which 292 cardiovascular deaths). Online HDF reduced the risk of all-cause mortality by 14 % (95 % CI: 1–25 %), and cardiovascular mortality by 23 % (95 % CI: 3–39 %). There was no evidence for a differential effect in subgroups. The largest survival benefit was for patients receiving the highest delivered convection volume (>23 L/1.73 m^2 BSA per session), with a multivariable-adjusted HR of 0.78 (95 % CI 0.62–0.98) for all-cause mortality and 0.69 (0.47–1.00) for cardiovascular mortality [29].

Summary and Conclusions

In recent years, several RCTs on online post-dilution HDF have been completed, and several meta-analysis on convective therapies have been performed. Despite the negative results of some RCTs, combination of study results in meta-analysis (both with aggregated study results and with individual patient data) suggest a survival benefit of about 15 % appears for patients treated with online HDF. The different studies do not show differential effects across various subgroups. Finally, in post-hoc analysis, the largest survival benefit was observed in patients receiving the highest delivered convection volume (>22-23 L/treatment/1.73m^2 BSA/session).

Teaching Points

- Studies in convective techniques differ widely in design, end points, patient numbers, treatment and comparison arms, and convection volume in the treatment arms.
- In the last decade, three large randomized controlled trials on online post-dilution hemodiafiltration primarily designed to assess effects on mortality have been performed: the Dutch CONvective TRansport Study (CONTRAST), the Turkish Hemodiafiltration Study and the Catalonian Hemodiafiltration Study (ESHOL).
- The CONTRAST-study and Turkish HDF study showed no significant survival benefit of hemodiafiltration, whereas the mortality risk was significantly lower in patients treated with hemodiafiltration in the ESHOL study (HR 0.70;95 % CI 0.53–0.92).
- In all three large RCTs, post-hoc (on-treatment) analysis showed a survival benefit of up to 40 % for patients treated with high-volume hemodiafiltration (convection volume >20–22 L/treatment).
- Trials seem simple, yet they are not. Results from trials can be biased when insufficient care is taken with respect to comparability between the

treatment arms. Issues such as comparability in natural history, procedures and measurements, changes in risk in patients during the trial, and selective loss to follow-up deserve attention in design of the trial, during the conduct of the trial, and in the statistical analysis.

- When the individual studies are biased, a meta-analysis is just pooling biased results, and thus does not bring the real answer any closer to the truth
- Two meta-analysis approaches are available: one is pooling aggregated results from publications, the other collects all the individual participant data (IPD) from all trials and has the analysis rerun. The latter is best for making adjustments and evaluating subgroup results.
- The definition of convective treatment in the different meta-analyses performed varies widely. Most meta-analyses include treatments with low convection volumes in the intervention arm.
- In both meta-analysis on aggregated results and individual pooled data meta-analysis of RCTs, the relative risk for mortality of online hemodiafiltration (as compared to hemodialysis) is about 0.83–0.86, indicating a 15 % lower mortality risk for patients treated with hemodiafiltration.
- An analysis on modern convective therapies should include only online convective treatments, achieving >20 L of convection volume per treatment.

References

1. Henderson LW, Colton CK, Ford CA. Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. J Lab Clin Med. 1975;85(3):372–91.
2. Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi E Trapianto. Kidney Int. 1999;55(1):286–93.
3. Jirka T, Cesare S, Di BA, Perera CM, Ponce P, Richards N, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis. Kidney Int. 2006;70(8):1524–5.
4. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int. 2006;69(11):2087–93.
5. Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, et al. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. Nephrol Dial Transplant. 2008;23(7):2337–43.
6. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009;4(12):1944–53.
7. Imamovic G, Hrvacevic R, Kapun S, Marcelli D, Bayh I, Grassmann A, et al. Survival of incident patients on high-volume online hemodiafiltration compared to low-volume online hemodiafiltration and high-flux hemodialysis. Int Urol Nephrol. 2014;46(6):1191–200.
8. Siriopol D, Canaud B, Stuard S, Mircescu G, Nistor I, Covic A. New insights into the effect of haemodiafiltration on mortality: the Romanian experience. Nephrol Dial Transplant. 2015; 30(2):294–301.

9. Canaud B, Bayh I, Marcelli D, Ponce P, Merello JI, Gurevich K, et al. Improved survival of incident patients with high-volume haemodiafiltration: a propensity-matched cohort study with inverse probability of censoring weighting. Nephron. 2015;129(3):179–88.
10. Canaud B, Barbieri C, Marcelli D, Bellocchio F, Bowry S, Mari F, et al. Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration. Kidney Int. 2015. doi.10.1038/ki.2015.139. (Epub ahead of print)
11. Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G, et al. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. Kidney Int. 1996;50(4):1293–302.
12. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. J Am Soc Nephrol. 2000;11(12):2344–50.
13. Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. Nephrol Dial Transplant. 2000;15 Suppl 1:43–8.
14. Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA, et al. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol. 2010;21(10): 1798–807.
15. Tessitore N, Santoro A, Panzetta GO, Wizemann V, Perez-Garcia R, Martinez AJ, et al. Acetate-free biofiltration reduces intradialytic hypotension: a European multicenter randomized controlled trial. Blood Purif. 2012;34(3–4):354–63.
16. Canaud B, Morena M, Leray-Moragues H, Chalabi L, Cristol JP. Overview of clinical studies in hemodiafiltration: what do we need now? Hemodial Int. 2006;10 Suppl 1:S5–12.
17. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.
18. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
19. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
20. Rabindranath KS, Strippoli GF, Roderick P, Wallace SA, MacLeod AM, Daly C. Comparison of hemodialysis, hemofiltration, and acetate-free biofiltration for ESRD: systematic review. Am J Kidney Dis. 2005;45(3):437–47.
21. Locatelli F. Comparison of hemodialysis, hemodiafiltration, and hemofiltration: systematic review or systematic error? Am J Kidney Dis. 2005;46(4):787–8.
22. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2013;28(11):2859–74.
23. Mostovaya IM, Blankestijn PJ, Bots ML, Covic A, Davenport A, Grooteman MP, et al. Clinical evidence on hemodiafiltration: a systematic review and a meta-analysis. Semin Dial. 2014; 27(2):119–27.
24. Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, et al. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. Am J Kidney Dis. 2014;63(6):954–67.
25. Grooteman MP, Blankestijn PJ, Nube MJ. Not all convective dialysis therapies are equal. Am J Kidney Dis. 2014;64(5):819–20.
26. Wang AY, Ninomiya T, Al-Kahwa A, Perkovic V, Gallagher MP, Hawley C, et al. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. Am J Kidney Dis. 2014;63(6):968–78.
27. Susantitaphong P, Jaber BL. Understanding discordant meta-analyses of convective dialytic therapies for chronic kidney failure. Am J Kidney Dis. 2014;63(6):888–91.

28. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58(2):809–17.
29. Peters SAE, Bots ML, Canaud B, Davenport A, Grooteman MPC, Kircelli F, et al. Haemodiafiltration and mortality in end stage kidney disease patients. A pooled individual participant data meta-analysis from four randomized controlled trials. Nephrol Dial Transplant 2015. doi:10.1093/ndt/gfv349.

Chapter 17
Hemodynamic Stability and Cardiovascular Effects of Convective Therapies

Jeroen P. Kooman, Frank M. van der Sande, and Karel M.L. Leunissen

Abstract This chapter addresses the acute and chronic cardiovascular effects of convective therapies. The most important acute cardiovascular complication in intermittent dialysis therapies is intra-dialytic hypotension (IDH) which causes patient discomfort, but is also related to end organ ischemia and mortality. The pathogenesis of IDH is multifactorial, in which both patient- and treatment-related factors are involved. The effect of the dialysis treatment on IDH is mediated by three factors: a decline in blood volume, an impaired reactivity of the resistance and capacitance vessels and myocardial contractility.

Various studies have shown that the incidence of IDH is reduced by the use of convective techniques. Available evidence suggests that the most important responsible factor for the positive hemodynamic effects of convective techniques is an improved reactivity of the resistance and capacitance vessels as compared to hemodialysis (HD). This phenomenon also appears to be at least partly mediated by thermal factors. Post-dilution hemodiafiltration (HDF) has an increased cooling effect as compared to HD due to additional heat loss from the infusion line. Smaller studies showed an equivalent incidence of IDH and hemodynamic response between HD and convective techniques after control for thermal factors. As for the chronic cardiovascular effects of convective therapies, available evidence does not suggest a major role of convective therapies on inter-dialytic blood pressure, arterial stiffness or left ventricular mass. Evidence on cardiovascular events and outcomes are as yet conflicting, one randomized study showing a positive effect of post-dilution on-line HDF on cardiovascular mortality and incidence of stroke, whereas other studies did not show a significant effect on cardiovascular outcomes. Future randomized studies, carefully controlled for thermal factors, are needed to fully establish the potential of convective techniques in preventing both short-and long-term cardiovascular complications in dialysis patients.

J.P. Kooman, MD, PhD (✉) • K.M.L. Leunissen, MD, PhD
Division of Nephrology, Department of Internal Medicine, University Hospital Maastricht,
PO Box 5800, Maastricht, Limburg 6202AZ, The Netherlands
e-mail: Jeroen.kooman@mumc.nl

F.M. van der Sande, MD, PhD
Division of Nephrology, Department of Internal Medicine,
Maastricht University Medical Center, Maastricht, Limburg, The Netherlands

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_17

Keywords Hemodiafiltration • Intra-dialytic hypotension • Vascular reactivity • Thermal balance • Arterial stiffness • Hypertension • Left ventricular hypertrophy • Cardiovascular mortality

Intradialytic Hypotension

Introduction

The most important acute complication of dialysis therapies is intra-dialytic hypotension (IDH). IDH is a frequently occurring phenomenon which can cause significant patient discomfort but can, in some cases, even lead to severe complications. IDH has been defined in different ways. By K/DOQI and the European Best Practice Guidelines (EBPG), IDH is defined as a decline in systolic blood pressure (BP) ≥20 mmHg or a decline in mean arterial pressure (MAP) by 10 mmHg versus baseline, associated with clinical events and need for nursing interventions [1, 2]. However, in the literature, also other definitions, e.g. based on the nadir BP have been proposed [3].

The incidence of IDH during hemodialysis is significant. Historically, IDH is assumed to occur in 20–30 % of dialysis sessions [4]. More recent surveys have addressed this issue in more detail. In a survey from Great Britain in 2,193 patients including 6,579 dialysis sessions, symptomatic IDH (defined as a sudden decline in BP, which required intravenous fluid replacement) occurred in 14.9 % of non-diabetic and 20.3 % of diabetic dialysis patients [5]. In a study from the US in 1,137 patients including 44,801 treatments [6], IDH (defined as an intradialytic decline in systolic BP by more than 30 mmHg to a level of less than 90 mmHg) occurred in 17.2 % of patients with a large intra-individual variability: whereas 25.1 % of patients did not experience IDH at all, in 16.2 % IDH occurred in more than 35 % of treatments. The incidence of IDH also varies between centers [7]. In a report based on audits in the Greater London area in the UK including 11 centers, the incidence of IDH varied between 7 % and 28 % of treatments.

In the largest survey available so far, Stefansson et al. studied records of 39,497 patients in the USRDS database during a 90 days assessment period. IDH, defined in line with the K/DOQI guidelines (≥20 mmHg fall in systolic BP plus ≥2 responsive measures) was observed in 31 % of patients at least once [8]. In a study in 1,409 patients of the HEMO cohort, the incidence of IDH according to the K/DOQI definition was 9.6 % [3]. Summarizing, even in contemporary dialysis treatment, IDH remains a common problem. However, it also becomes clear that the definition of IDH used in the literature varies widely.

The consequences of IDH are substantial. On the short term, IDH leads to clinical symptoms such as nausea, vomiting, cramps and cardiovascular collapse. It has also been involved in the pathogenesis of vascular access thrombosis [9]. At a subclinical level, indirect evidence suggests that IDH as such may contribute to reversible regional myocardial dysfunction ("stunning") as well as circulating endotoxemia due to splanchnic hypoperfusion [10–12].

In addition, various [3, 8, 13] reports found a relation between IDH and outcome. In a study in 1,244 dialysis patients, Shoji et al. observed that a fall in intra-dialytic systolic BP of more than 40 mmHg, was associated with an increase in 2-years mortality as compared to patients with a lower intra-dialytic fall in systolic BP after adjustment for age, gender, diabetic status, serum creatinine, ultrafiltration per body weight, and body weight after HD [13]. In a study by Stefansson et al. the occurrence of one or more episodes of IDH during a 90 day period was associated with an increased risk for all-cause and cardiovascular mortality, as well as for major adverse cardiac events during a mean follow-up time of 398 days [8]. Despite correction for comorbid factors, these observations do not necessarily imply causation, although for instance, repetitive cardiac stunning might result in persistent left ventricular dysfunction and is also in itself an important risk factor for mortality [14, 15].

The relation between IDH and outcome also appears to depend on its definition. In a recent analysis in 11,801 patients, the strongest association with mortality was observed with a nadir in systolic BP of 90 mmHg or less in patients with pre-dialytic systolic BP below 160 mmHg. In patients with pre-dialytic systolic BP levels of 160 mmHg or higher, the strongest association was observed with nadir systolic BP levels below 100 mmHg. Unlike the results of Shoji et al. [13], in this study, symptoms, interventions or the magnitude of the decline in BP per se were not associated with outcome [3].

Nevertheless, regardless of the differences in the literature and the uncertainties with regard to causation, it is well established that IDH is an important risk factor for mortality in dialysis patients and that both for this reason, as well as to prevent patient discomfort, its prevention is of great clinical importance.

Pathophysiology of IDH

The pathophysiology of IDH is multifactorial, but three major components can be distinguished [2, 16]. In analogy to hypovolemic shock, the first driver is the decline in circulating blood volume leading to a decline in venous return to the heart [17, 18]. However, in contrast to previously healthy persons, in whom a decline in plasma volume up to 15 % (and in some cases up to 25 %) is not associated with significant clinical features, IDH can occur at a much lower decline in blood volume. In a survey in 60 IDH-prone patients, intra-morbid events (two out of three related to IDH) occurred at a decline in relative blood volume varying between 2 % and 29 % [19].

The fact that IDH may occur at a much lower decline in blood volume as compared to healthy subjects indicates that the normal compensatory response to hypovolemia can be disturbed in dialysis patients. The acute compensatory response to hypovolemia, subsequently activated by low and high pressure receptors in the cardiovascular system, results in an increase in myocardial contractility and heart rate, as well as an increase in peripheral arterial and venous tone through sympathetic activation [17, 20].

In dialysis patients, both patient as well as treatment related factors may interfere with the hemodynamic response during dialysis. Patient related-factors contributing to IDH, which will not be discussed in detail further in this chapter, include factors such as age and dialysis vintage, as well as structural cardiovascular abnormalities, such as a reduction in left ventricular systolic or diastolic function, a reduction in compliance of the venous system, and autonomous neuropathy [2, 6, 14, 21, 22]. Treatment related factors contributing to the occurrence or prevention of IDH can be conceptually summarized as factors influencing respectively blood volume, vascular reactivity and myocardial contractility [2].

Ultrafiltration volume, the major determinant of the decline in blood volume during dialysis [23], is mainly influenced by ultrafiltration rate, a resultant of the inter-dialytic weight gain and treatment time. Various studies [6, 8] showed inter-dialytic weight gain to be important predictors of IDH. Next to ultrafiltration, an important treatment-related determinant of the fall in blood volume is the sodium concentration of the dialysate [24].

When blood volume declines, an adequate vascular reactivity is of pivotal importance to maintain BP. This reactivity concerns both a constriction of the resistance vessels, leading to an increase in systemic vascular resistance, as well as a constriction of the capacitance vessels. The latter contain 80 % of circulating blood volume, and mobilization of so-called "unstressed" (i.e. hemodynamically inactive blood volume [20]) allows for maintenance of venous return and preservation of cardiac output despite a fall in blood volume [25]. During dialysis, this process may be impaired. In search for the pathogenesis of this phenomenon, it has become clear that thermal factors play a major role.

The dialysis membrane is an efficient heat exchanger due to the close and continuous contact between the blood and dialysis fluid. An important determinant of body temperature changes during dialysis is therefore the ratio between the pre-dialytic body temperature of the patient and the dialysate temperature [26, 27]. It has been shown that core temperature generally increases in patients with a dialysate temperature of 37–37.5 °C [26, 28, 29], which may interfere with the normal reactivity of the vascular system by inducing vasodilation of the cutaneous blood vessels in order to remove the excess heat. One of the most potent methods to prevent IDH is cooling of the patient by reducing the dialysate temperature [30, 31], which is mainly explained by its beneficial effect on vascular reactivity [29]. In a systematic review, the incidence of IDH with the use of cool dialysis was reduced by 7.1 times [32].

Interestingly, core temperature increases during dialysis even without addition of heat from the extracorporeal circuit [33], which suggests that, apart from the effects of dialysate temperature, the dialysis treatment itself contributes to the increase in core temperature. Available literature suggests that both an initial reduction in heat loss from the skin due to peripheral vasoconstriction in response to a decline in blood volume (later followed by vasodilation), but also as yet unidentified factors related to the hemodialysis procedure per se play a role in the increase in core temperature during dialysis [33–35]. Without additional removal of thermal energy from the extracorporeal circuit, a mean increase in arterial temperature of 0.47 °C was observed during dialysis [36].

The amount of thermal energy which needs to be removed in order to keep body temperature stable (isothermic) during dialysis is substantial, and has been assessed by monitoring extracorporeal heat flow (J_{ex}) during dialysis by a specific device (Blood Temperature Monitor®). J_{ex} is calculated by the formula: $J_{ex} = -c\rho\left(T_{art} - T_{ven}\right)*\left(Q_b - UFR\right)$[1] [35]. The product c ρ (3.81 J/°C/m^3) refers to the heat capacity and density of blood, T_{art} and T_{ven} to respectively the temperature in the arterial and venous blood line, Q_b to extracorporeal blood flow rate and UFR to ultrafiltration rate. One study found a J_{ex} of −0.25 W/kg during isothermic treatments, corresponding to 24 % of the resting energy expenditure, whereas in another study a mean J_{ex} of −17.9 W was observed [33, 36]. Whether it suffices to maintain body temperature or whether further cooling is needed to maintain optimal hemodynamic stability during dialysis remains to be determined, although only small, albeit significant differences in the blood pressure decline during dialysis were observed between isothermic treatments (in which core temperature was kept stable) and dialysis during which the core temperature was decreased by 0.5 °C [37].

Regarding cardiac contractility, in important treatment-related factor is dialysate calcium [38], which may have relevance for the intra-dialytic blood pressure course [38, 39]. In addition, the dialysis procedure itself, but especially ultrafiltration may induce myocardial stunning [14, 15]. Whether the latter phenomenon also plays a role in the pathogenesis of IDH remains to be determined.

IDH During HDF

The first study showing a difference in the hemodynamic response between convective therapies (conventional hemofiltration [HF] with infusion of bags) and HD was already published in 1980 by Quellhorst et al. [40]. (These results were confirmed in later studies with conventional HDF [41]. However, different studies also showed a reduction in IDH with on line convective therapies as compared to hemodialysis, both for on-line HF as well as HDF [42–44]. In the largest study so far (ESHOL study), in which 906 patients were randomized to post-dilution o-HDF or HD with a mean follow up of 1.9 years, the incidence rate ratio of IDH with on-line HDF (oHDF) was 0.72 [CI 0.68–0.77] as compared to HD [43]. In this study, IDH was not clearly defined, but the results are of significant relevance given the reduction in CV mortality and stroke observed in this study with the use of HDF. In a multicenter study in 146 patients randomly allocated to either pre-dilution oHDF (n = 40), on-line HF (n = 36) or HD (n = 70), a reduction [44] of IDH was observed with both o-HF (OR 0.69; 95 % confidence interval 0.51–0.92) as well as o-HDF (OR 0.46, 95 % confidence interval 0.33–0.63). In this study, IDH was defined as a rapid symptomatic fall of systolic BP by at least 30 mmHg or that required nursing and/or medical intervention. In a meta-analysis of RCT published in 2013 in which 1,006 patients divided over 12 study arms were pooled, the relative risk of IDH with convective

[1] A negative Jex reflects heat flow from the patient to the extracorporeal system (“cooling”)

therapies (which also included the use of high flux treatments) was 0.55, 95 % CI 0.35, 0.87, P=0.01) as compared to low-flux HD [45]. Comparable results (RR, 0.49; 95 % CI, 0.30–0.81) in which HF or HDF therapies were compared to HD were observed in a later meta-analysis [46] in five trials with in total 1,259 participants, as well as in another meta-analysis (RR 0.72 [CI 0.66–0.88]) [47]. Summarizing, there is extensive evidence that IDH is reduced by the use of convective treatments.

Effects of Convective Therapies on the Pathophysiologic Determinants of IDH

Whereas the benefits of HDF on hemodynamic instability have been independently shown in various trials, the mechanism behind this effect has not been completely elucidated. Previous reports with conventional HF suggested that, possibly due to an increase in the Donnan effect due to protein coating of the dialyzer, sodium removal was lower during convective therapies [48, 49], which could result in improved blood volume preservation [50, 51]. However, other studies with on-line HF or HDF [52] did not observe differences in sodium removal, blood volume preservation, or body water compartments [50, 53, 54] between convective therapies and on-line convective therapies. In contrast, one study even observed a larger decline in blood volume during post-dilution on on-line HDF as compared to HD [55]. With regard to myocardial contractility, no study as yet addressed potential differences between HD and convective therapies.

The main mechanism affected by convective therapies appears to be an improved vascular reactivity [56]. Studies from the early 1980s showed an increase in systemic vascular resistance as well as plasma noradrenaline levels during conventional HF as compared to HD [40, 57, 58]. These results were later confirmed by others [59, 60], showing both an increase in peripheral vascular resistance as well as venous tone. The mechanisms behind the differences in vascular response between convective therapies and HD have not been definitely elucidated. Various mechanisms, such as differences in removal of larger molecular weight vasoactive substances such as calcitonin-related gene peptide, or ouabain-like factors, or a reduction in inflammatory mediators have been suggested [56, 61–63]. However, most available evidence suggests an important role of extracorporeal cooling as an important contributory factor to the improved hemodynamic response during convective strategies [55, 59].

Effects of Convective Therapies on Thermal Balance

As discussed previously, the temperature in the venous blood line (T_{ven}) is an important contributor to the extracorporeal heat flow rate J_{ex}. T_{ven} is dependent on the temperature of the dialysate, and the heat loss from the venous line to the

environment (which is approximately 7–15 W) [35, 64]. From this, it becomes clear that, irrespective of dialysate temperature, post-dilution HDF leads to additional cooling of the patient because of heat loss from the infusion line, next to the heat loss from the venous blood lines. This has been quantified in the study of Donauer et al. in which mean J_{ex} was −5.4 W during HD and −16.6 W during post-dilution on-line HDF with a mean dialysate/infusate temperature of 36.8 °C and an infusion rate of 50 ml/min [55]. In this study, the rise in mean blood temperature in the arterial line was significantly higher during HD (0.39 °C) as compared to on-line HDF (0.26 °C). In order to achieve the same J_{ex} during HD as compared to on-line HDF, the dialysate temperature had to be lowered to a mean of 35.6 °C in order to achieve the same J_{ex} as post-dilution on-line HDF. It should be noted that the infusion rate in this study was substantially less as compared to recent recommendations [65]. However, in a more recent study, mean J_{ex} was 16.2 W during post-dilution on-line HDF with a mean infusion rate of 59 ml/min and a dialysate temperature between 35.5 and 36.5 °C [53]. The thermal effects are different for pre-dilution on-line HDF, where this additional heat loss does not play a role because the infusion fluid enters the blood stream before the dialyzer. This was confirmed by a study comparing pre-dilution HDF with HD, during which the body temperature of the patient was kept stable (isothermic) by the feedback module of the Blood temperature monitor®. During a 4.5 h treatment, the mean energy which needed to be removed to allow an isothermic treatment was 155 kJ during HD and 135 kJ during pre-dilution on-line HDF, corresponding to an approximate J_{ex} of 9.6 and 8.3 W respectively [66].

With regard to the other, less commonly used convective strategies, no detailed in vivo data on thermal balance are available. For post-dilution on-line HF, the cooling effect will likely be larger as compared to HD with an equivalent dialysate temperature, because the additional heat exchange due to contact between blood and dialysate does not take place and because of the heat loss through the infusion line, as discussed previously for oHDF [46]. For pre-dilution HF, the cooling effect will likely be less pronounced because the infusion volumes are generally high and because the additional cooling due to the venous line does not take place [46]. In an in vitro study, the estimated thermal balance (expressed as kJ/h) was −35 kJ/h with pre-dilution HF (−9.7 W) at an infusate temperature of 37 °C, as compared to 72 kJ/h with post-dilution HF (−20.0 W, −10 kJ/h (−2.8 W) with conventional HD and −170 kJ/h (−47.2 W) with cool dialysis (35.5 °C). However, translation from in vitro to in vivo data is hazardous because regulation of "arterial" temperature, which occurs constantly in vivo, is not possible in the in vitro setting.

The heat loss may be larger with conventional convective techniques given the fact that the temperature of the infusion fluid is generally lower as compared to on-line convective therapies, with fluids mostly infused at room temperature [35]. This explains the finding that during conventional HDF, the cooling effect was dependent upon the infusion volume. In a crossover study in 12 patients, mean J_{ex} was comparable between HD 35.5 °C (−26.6 W) and post-dilution HDF with an

infusion rate of 2.5 L/h (mean −25.3 W) and was significantly more negative compared with HD 37.5 °C (−3.5 W) and HDF at an infusion rate of 1 L/h (−15.9 W) [41].

The Relation between Extracorporeal Cooling and the Hemodynamic Response to HDF

These thermal effects appear to have a major impact on the hemodynamic stability during treatments. In a crossover study in 17 patient with frequent IDH, in which 25 treatments were compared between 3 different treatment settings the incidence of IDH (defined as a decline in systolic BP below 100 mmHg in the presence of symptoms) was 40 % higher during HD as compared to on-line HDF without correction for this additional energy loss, whereas no difference in hypotensive episodes between HD and on-line HDF was observed when the dialysate was additionally cooled during HD (4 % during both modalities), in order to achieve a comparable energy balance [55], see Fig. 17.1. In addition, in a single treatment study, no differences in the hemodynamic response to HD and on-line HDF were observed with comparable negative J_{ex} [53], see Fig. 17.2. Another study in 12 dialysis patients found a significantly larger decline in BP during HD with a dialysate temperature of 37.5 °C as compared to conventional HDF, but no difference in the BP fall between HDF and cool dialysis (temperature 35.5 °C) [41]. In earlier study, by van Kuijk et al. vascular reactivity was clearly different between HD and conventional HF, when the latter was associated with a significant cooling effect whereas no difference was observed when the temperature of the infusion fluid was heated in order to obtain comparable thermal effects [59]. In a non-controlled prospective study in which 44 patients on cooled HD (median dialysate temperature 35 °C) were compared to 34 patients on post-dilution oHDF (median dialysate/infusate temperature 36 °C, infusion volume 65–85 ml/min), the incidence of IDH was even higher in the oHDF group (25.9 % versus 16.5 %; $p=0.01$) [62]. In a crossover study in 12 patients, no difference in change in cardiac output, BP or total peripheral resistance was observed between pre-dilution on-line HDF and HD under thermal controlled conditions [66]. In contrast to these findings, in the study of Locatelli, IDH was significantly reduced despite the fact that pre-dilution HDF was used [44]. As discussed previously, theoretically, this should have resulted in the comparable thermal balance between the convective techniques and HD, although data on this aspect were not available. Also in the ESHOL study, in which a significant reduction in IDH was observed with post-dilution HDF, which has likely resulted in significant cooling effects, unfortunately no data on thermal effects of the different modalities were available [43].

Thus, there is substantial clinical evidence for an important effect of thermal balance as an important contributing factor to the improved hemodynamic stability during convective therapies. Whether additional factors are also involved

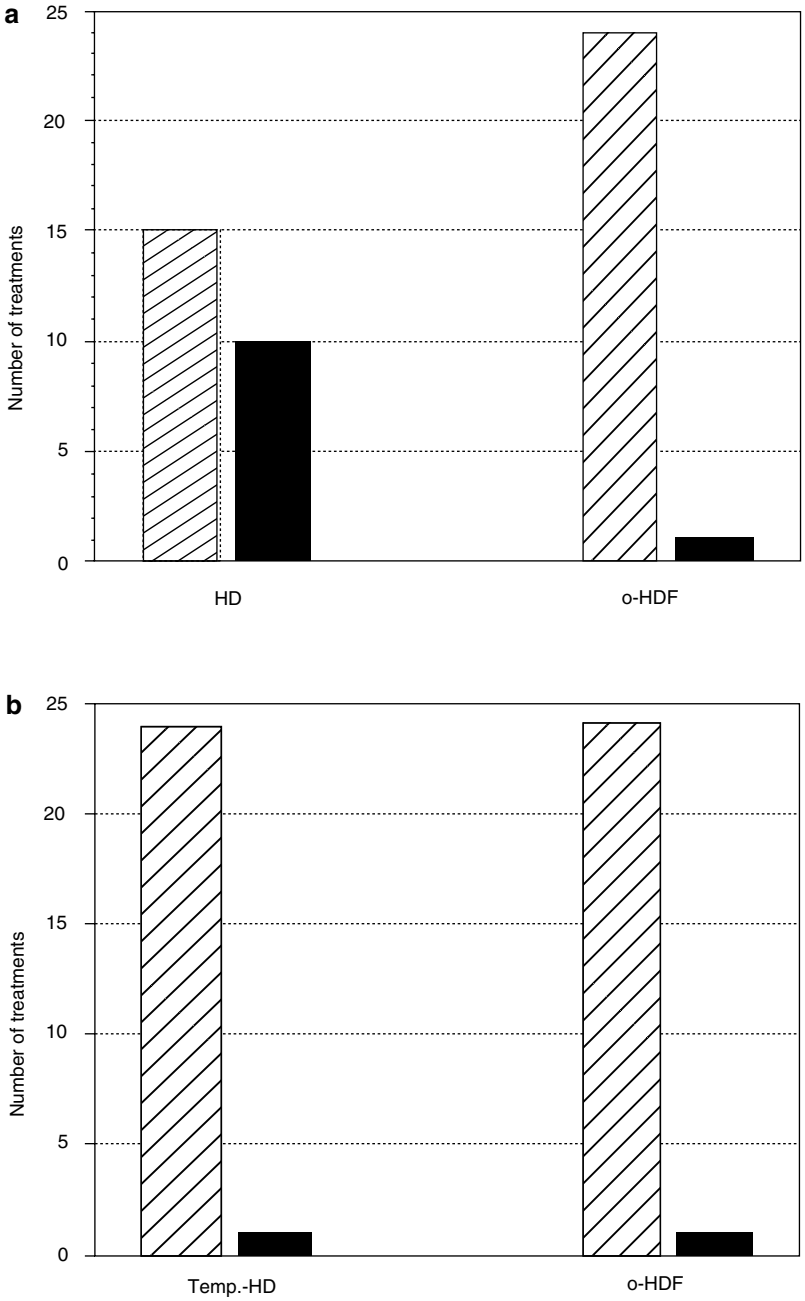


Fig. 17.1 This figure shows that the incidence of IDH is significantly reduced by on line HDF as compared to HD without correction for thermal energy balance (**a**), but a comparable reduction in IDH during HD when both treatments were matched for thermal balance (Temp-HD) (**b**) (Reprinted from Donauer et al. [55]. With permission from Oxford University Press)

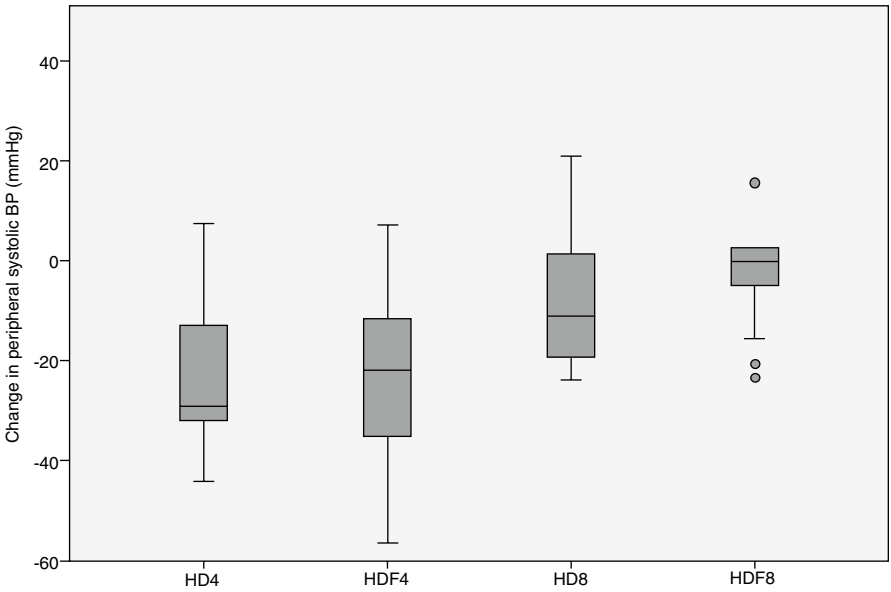


Fig. 17.2 Figure showing that the change in systolic blood pressure (*BP*) during treatment was more dependent on the duration of the treatment than on the modality choice of HD (mean dialysate temperature 35.9 °C) or on-line HDF. The number behind the modalities reflect the treatment duration in hours (Reprinted from Cornelis et al. [53]. With permission from Elsevier)

in the reduction of IDH during convective therapies should be investigated in future randomized trials with strict control of thermal balance between HD and HDF.

Long Term Effects on Cardiovascular Parameters

Cardiovascular events are the most important contributor to the greatly increased risk of mortality in dialysis patients [67]. Uncontrolled hypertension and structural cardiovascular abnormalities such as increased arterial stiffness and left ventricular hypertrophy are important risk factors for mortality in dialysis patients [68–70]. It has been suggested that convective techniques are associated with improved cardiovascular outcomes, but also with an improved BP regulation and cardiovascular structure due to increased removal of larger molecular weight uremic toxins and vasoactive substances such as asymmetric dimethylarginine (ADMA) [71]. In the following paragraphs, the available evidence for an effect of convective techniques on BP regulation, cardiovascular structure and outcomes will be summarized.

Hypertension

Earlier reports suggested an improved regulation of hypertension with the use of conventional HF [72]. However, these results were not confirmed in later randomized studies with longer follow-up durations. Beerenhout et al. did not observe a difference in BP regulation, assessed by 48-h ambulatory BP measurements with the use of pre-dilution on-line HF [71]. Notably, in this study, also no effect of oHF on serum levels of ADMA was observed. Neither in the ESHOL nor in the CONTRAST an effect of oHDF on BP were observed [43, 73], whereas in the Turkish on-line HDF study significantly higher time averaged systolic BP levels were observed with oHDF (129 ± 13 versus 126 ± 13 mmHg, P = 0.001) as compared to HD [74]. Also a cross-sectional study did not show differences in pre-dialytic BP between patients treated with HD or oHDF [62]. Therefore, there is at present no evidence for a direct positive additional effect on inter-dialytic BP regulation and hypertension control. It cannot be excluded that the earlier positive results of conventional HF on BP resulted from a better volume regulation due to an improved hemodynamic tolerance during HF.

Structural Cardiovascular Parameters

Few studies have assessed the effect of convective therapies on structural cardiovascular parameters. In two observational studies, no differences in pulse wave velocity, as a marker of arterial stiffness, were observed between patients on oHDF and matched HD patients [75, 76].

Two randomized studies have studied the effect of convective techniques on structural cardiovascular parameters. In a study in patients comparing on-line HF with low-flux HD during a follow-up time of 1 year, arterial stiffness or left ventricular mass did not differ between the groups [71]. Also in a subgroup of the CONTRAST study, no differences in arterial stiffness or left ventricular mass were observed between the groups randomized either to low-flux HD or post-dilution HDF [73].

Cardiovascular Outcomes

Three large randomized controlled trials were recently published which, in addition to all-cause mortality, also assessed the risk of cardiovascular mortality and/or events.

The CONTRAST study did not find a difference in the composite cardiovascular outcomes between low-flux HD and post-dilution on-line HDF (hazard ratio, 1.07;

95 % confidence interval, 0.83–1.39) [77]. Also in the Turkish OL-HDF study, comparing on-line HDF with high flux HD, no difference in cardiovascular mortality or events was observed in the primary analysis, although an improved cardiovascular outcome was observed in the subgroup which achieved higher substitution volumes [74]. In the ESHOL study, a near significant difference in cardiovascular mortality (HR, 0.67; 95 % CI, 0.44–1.02; P = 0.06) between post-dilution on-line HDF and high-flux dialysis was observed in the primary analysis. A reduction in stroke risk was a significant contributor to the reduced cardiovascular mortality in this study [43]. The reason for the improved cardiovascular outcome in this study was not clear, although the authors hypothesized that a reduction in systemic inflammation might be involved. However, it should be noted that in this study also a significant reduction in IDH was observed, which might have contributed to lesser variations in cerebral perfusion.

Also in systematic reviews, the effect of convective techniques on cardiovascular outcomes has yielded conflicting results. In one analysis, no effect of convective techniques (defined as filtration techniques and high-flux dialysis) on cardiovascular outcomes was observed as compared to low-flux dialysis [46]. Another systematic review observed a reduction in cardiovascular mortality, but not in non-fatal cardiovascular events between convective techniques (including HDF, HD and acetate-free biofiltration) as compared to HD techniques [47].

Summarizing, there is no solid evidence for a beneficial effect of convective techniques on either inter-dialytic BP regulation or structural cardiovascular parameters. The effect on convective techniques on cardiovascular outcome is conflicting. One randomized study observed a near significant reduction in cardiovascular outcome and a reduction in stroke incidence. More studies are needed to definitely address the effect of convective techniques on cardiovascular outcome in dialysis patients.

Teaching Points

- The most important acute cardiovascular complication in intermittent dialysis therapies is intra-dialytic hypotension (IDH), which is related to end organ ischemia and mortality.
- The effect of the dialysis treatment on IDH is mediated by three factors: a decline in blood volume, impaired reactivity of the resistance and capacitance vessels and myocardial contractility.
- The incidence of IDH is reduced by the use of convective techniques.
- The most important responsible factor for the positive hemodynamic effects of convective techniques is an improved reactivity of the resistance and capacitance vessels as compared to hemodialysis (HD). This phenomenon appears to be at least partly mediated by thermal factors.
- Post-dilution hemodiafiltration (HDF) has an increased cooling effect as compared to HD due to additional heat loss from the infusion line.

- Available evidence does not suggest a major role of convective therapies on inter-dialytic blood pressure, arterial stiffness or left ventricular mass.
- Evidence on the effect of HDF on cardiovascular outcome is yet conflicting.
- Future randomized studies, carefully controlled for thermal factors, are needed to fully establish the potential of high-volume post-dilution HDF in preventing both short-and long-term cardiovascular complications in dialysis patients.

References

1. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45(4 Suppl 3):S1–153.
2. Kooman J, Basci A, Pizzarelli F, Canaud B, Haage P, Fouque D, Konner K, Martin-Malo A, Pedrini L, Tattersall J, Tordoir J, Vennegoor M, Wanner C, ter Wee P, Vanholder R. EBPG guideline on haemodynamic instability. Nephrol Dial Transplant. 2007;22 Suppl 2:ii22–44.
3. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of Mortality Risk with Various Definitions of Intradialytic Hypotension. J Am Soc Nephrol. 2015;26:724–34.
4. Palmer BF, Henrich WL. Recent advances in the prevention and management of intradialytic hypotension. Nephrol Dial Transplant. 2005;20:1155–63.
5. Davenport A, Cox C, Thuraisingham R. Blood pressure control and symptomatic intradialytic hypotension in diabetic haemodialysis patients: a cross-sectional survey. Nephron Clin Pract. 2008;109:c65–71.
6. Sands JJ, Usvyat LA, Sullivan T, Segal JH, Zabetakis P, Kotanko P, Maddux FW, Diaz-Buxo JA. Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. Hemodial Int. 2014;18:415–22.
7. Davenport A, Cox C, Thuraisingham R. Achieving blood pressure targets during dialysis improves control but increases intradialytic hypotension. Kidney Int. 2008;73:759–64.
8. Stefánsson BV, Brunelli SM, Cabrera C, Rosenbaum D, Anum E, Ramakrishnan K, Jensen DE, Stålhammar NO. Intradialytic hypotension and risk of cardiovascular disease. Clin J Am Soc Nephrol. 2014;9:2124–32.
9. Chang TI, Paik J, Greene T, et al. Intradialytic hypotension and vascular access thrombosis. J Am Soc Nephrol. 2011;22:1526–33.
10. Jefferies HJ, Crowley LE, Harrison LE, Szeto CC, Li PK, Schiller B, Moran J, McIntyre CW. Circulating endotoxaemia and frequent haemodialysis schedules. Nephron Clin Pract. 2014;128:141–6.
11. Jefferies HJ, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). Clin J Am Soc Nephrol. 2011;6:1326–32.
12. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4:914–20.
13. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int. 2004;66:1212–20.
14. Assa S, Hummel YM, Voors AA, Kuipers J, Westerhuis R, de Jong PE, Franssen CF. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. Clin J Am Soc Nephrol. 2012;7:1615–23.

15. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009;4:1925–31.
16. van der Sande FM, Kooman JP, Leunissen KM. Intradialytic hypotension – new concepts on an old problem. Nephrol Dial Transplant. 2000;15:1746–8.
17. Worthley LI. Shock: a review of pathophysiology and management. Part I. Crit Care Resusc. 2000;2:55–65.
18. Hardaway RM. Monitoring of the patient in a state of shock. Surg Gynecol Obstet. 1979;148:339–52.
19. Barth C, Boer W, Garzoni D, Kuenzi T, Ries W, Schaefer R, Schneditz D, Tsobanelis T, van der Sande F, Wojke R, Schilling H, Passlick-Deetjen J. Characteristics of hypotension-prone haemodialysis patients: is there a critical relative blood volume? Nephrol Dial Transplant. 2003;18:1353–60.
20. Funk DJ, Jacobsohn E, Kumar A. The role of venous return in critical illness and shock-part I: physiology. Crit Care Med. 2013;41:255–62.
21. Ritz E, Rambausek M, Mall G, Ruffmann K, Mandelbaum A. Cardiac changes in uraemia and their possible relationship to cardiovascular instability on dialysis. Nephrol Dial Transplant. 1990;5 Suppl 1:93–7.
22. Kooman JP, Wijnen JA, Draaijer P, van Bortel LM, Gladziwa U, Peltenburg HG, Struyker-Boudier HA, van Hooff JP, Leunissen KM. Compliance and reactivity of the peripheral venous system in chronic intermittent hemodialysis. Kidney Int. 1992;41:1041–8.
23. Mann H, Ernst E, Gladziwa U, Schallenberg U, Stiller S. Changes in blood volume during dialysis are dependent upon the rate and amount of ultrafiltrate. ASAIO Trans. 1989;35: 250–2.
24. Brummelhuis WJ, van Geest RJ, van Schelven LJ, Boer WH. Sodium profiling, but not cool dialysate, increases the absolute plasma refill rate during hemodialysis. ASAIO J. 2009; 55:575–80.
25. Kooman JP, Gladziwa U, Böcker G, van Bortel LM, van Hooff JP, Leunissen KM. Role of the venous system in hemodynamics during ultrafiltration and bicarbonate dialysis. Kidney Int. 1992;42:718–26.
26. van der Sande FM, Kooman JP, Burema JH, Hameleers P, Kerkhofs AM, Barendregt JM, Leunissen KM. Effect of dialysate temperature on energy balance during hemodialysis: quantification of extracorporeal energy transfer. Am J Kidney Dis. 1999;33:1115–21.
27. Fine A, Penner B. The protective effect of cool dialysate is dependent on patients' predialysis temperature. Am J Kidney Dis. 1996;28:262–5.
28. Provenzano R, Sawaya B, Frinak S, Polaschegg HD, Roy T, Zasuwa G, Dumler F, Levin NW. The effect of cooled dialysate on thermal energy balance in hemodialysis patients. ASAIO Trans. 1988;34:515–8.
29. van der Sande FM, Gladziwa U, Kooman JP, Böcker G, Leunissen KM. Energy transfer is the single most important factor for the difference in vascular response between isolated ultrafiltration and hemodialysis. J Am Soc Nephrol. 2000;11:1512–7.
30. Schneditz D, Ronco C, Levin N. Temperature control by the blood temperature monitor. Semin Dial. 2003;16:477–82.
31. Maggiore Q, Dattolo P, Piacenti M, Morales MA, Pelosi G, Pizzarelli F, Cerrai T. Thermal balance and dialysis hypotension. Int J Artif Organs. 1995;18:518–25.
32. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. Nephrol Dial Transplant. 2006;21:1883–98.
33. van der Sande FM, Rosales LM, Brener Z, Kooman JP, Kuhlmann M, Handelman G, Greenwood RN, Carter M, Schneditz D, Leunissen KM, Levin NW. Effect of ultrafiltration on thermal variables, skin temperature, skin blood flow, and energy expenditure during ultrapure hemodialysis. J Am Soc Nephrol. 2005;16:1824–31.
34. Schneditz D, Rosales L, Kaufman AM, Kaysen G, Levin NW. Heat accumulation with relative blood volume decrease. Am J Kidney Dis. 2002;40:777–82.
35. Schneditz D. Temperature and thermal balance in hemodialysis. Semin Dial. 2001;14: 357–64.

36. Maggiore Q, Pizzarelli F, Santoro A, Panzetta G, Bonforte G, Hannedouche T, Alvarez de Lara MA, Tsouras I, Loureiro A, Ponce P, Sulkovà S, Van Roost G, Brink H, Kwan JT, Study Group of Thermal Balance and Vascular Stability. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. Am J Kidney Dis. 2002;40:280–90.
37. van der Sande FM, Wystrychowski G, Kooman JP, Rosales L, Raimann J, Kotanko P, Carter M, Chan CT, Leunissen KM, Levin NW. Control of core temperature and blood pressure stability during hemodialysis. Clin J Am Soc Nephrol. 2009;4(1):93–8.
38. van der Sande FM, Cheriex EC, van Kuijk WH, Leunissen KM. Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. Am J Kidney Dis. 1998;32:125–31.
39. Gabutti L, Bianchi G, Soldini D, Marone C, Burnier M. Haemodynamic consequences of changing bicarbonate and calcium concentrations in haemodialysis fluids. Nephrol Dial Transplant. 2009;24:973–81.
40. Quellhorst E, Schuenemann B, Hildebrand U, Falda Z. Response of the vascular system to different modifications of haemofiltration and haemodialysis. Proc Eur Dial Transplant Assoc. 1980;17:197–204.
41. van der Sande FM, Kooman JP, Konings CJ, Leunissen KM. Thermal effects and blood pressure response during postdilution hemodiafiltration and hemodialysis: the effect of amount of replacement fluid and dialysate temperature. J Am Soc Nephrol. 2001;12:1916–20.
42. Altieri P, Sorba G, Bolasco P, Asproni E, Ledebo I, Cossu M, Ferrara R, Ganadu M, Cadinu F, Serra G, Cabiddu G, Sau G, Casu D, Passaghe M, Bolasco F, Pistis R, Ghisu T, Second Sardinian Multicentre Study. Predilution haemofiltration – the Second Sardinian Multicentre Study: comparisons between haemofiltration and haemodialysis during identical Kt/V and session times in a long-term cross-over study. Nephrol Dial Transplant. 2001;16:1207–13.
43. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A, ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
44. Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA, Basile C, David S, Feriani M, Montagna G, Di Iorio BR, Memoli B, Cravero R, Battaglia G, Zoccali C. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol. 2010;21:1798–807.
45. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2013;28:2859–74.
46. Wang AY, Ninomiya T, Al-Kahwa A, Perkovic V, Gallagher MP, Hawley C, Jardine MJ. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. Am J Kidney Dis. 2014;63:968–78.
47. Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, Strippoli GF. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. Am J Kidney Dis. 2014;63:954–67.
48. Pedrini LA, Ponti R, Faranna P, Cozzi G, Locatelli F. Sodium modeling in hemodiafiltration. Kidney Int. 1991;40:525–32.
49. de Vries PM, Olthof CG, Solf A, Schuenemann B, Oe PL, Quellhorst E, Schneider H, Donker AJ. Fluid balance during haemodialysis and haemofiltration: the effect of dialysate sodium and a variable ultrafiltration rate. Nephrol Dial Transplant. 1991;6:257–63.
50. Kumar S, Khosravi M, Massart A, Potluri M, Davenport A. Haemodiafiltration results in similar changes in intracellular water and extracellular water compared to cooled haemodialysis. Am J Nephrol. 2013;37:320–4.
51. Quellhorst E, Schuenemann B, Hildebrand U. How to prevent vascular instability: haemofiltration. Proc Eur Dial Transplant Assoc. 1981;18:243–9.
52. Beerenhout C, Dejagere T, van der Sande FM, Bekers O, Leunissen KM, Kooman JP. Haemodynamics and electrolyte balance: a comparison between on-line pre-dilution haemofiltration and haemodialysis. Nephrol Dial Transplant. 2004;19:2354–9.

53. Cornelis T, van der Sande FM, Eloot S, Cardinaels E, Bekers O, Damoiseaux J, Leunissen KM, Kooman JP. Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. Am J Kidney Dis. 2014;64:247–56.
54. Caplin B, Alston H, Davenport A. Does online haemodiafiltration reduce intra-dialytic patient symptoms? Nephron Clin Pract. 2013;124:184–90.
55. Donauer J, Schweiger C, Rumberger B, Krumme B, Böhler J. Reduction of hypotensive side effects during online-haemodiafiltration and low temperature haemodialysis. Nephrol Dial Transplant. 2003;18:1616–22.
56. Santoro A, Mancini E, Zucchelli P. The impact of haemofiltration on the systemic cardiovascular response. Nephrol Dial Transplant. 2000;15 Suppl 2:49–54.
57. Baldamus CA, Ernst W, Lysaght MJ, Shaldon S, Koch KM. Hemodynamics in hemofiltration. Int J Artif Organs. 1983;6(1):27–31.
58. Baldamus CA, Ernst W, Frei U, Koch KM. Sympathetic and hemodynamic response to volume removal during different forms of renal replacement therapy. Nephron. 1982;31(4): 324–32.
59. van Kuijk WH, Hillion D, Savoiu C, Leunissen KM. Critical role of the extracorporeal blood temperature in the hemodynamic response during hemofiltration. J Am Soc Nephrol. 1997;8:949–55.
60. Fox SD, Henderson LW. Cardiovascular response during hemodialysis and hemofiltration: thermal, membrane, and catecholamine influences. Blood Purif. 1993;11:224–36.
61. Henderson LW. Hemodynamic instability during different forms of dialysis therapy: do we really know why? Blood Purif. 1996;14:395–404.
62. Pinney JH, Oates T, Davenport A. Haemodiafiltration does not reduce the frequency of intradialytic hypotensive episodes when compared to cooled high-flux haemodialysis. Nephron Clin Pract. 2011;119:c138–44.
63. Mora-Bravo FG, De-La-Cruz G, Rivera S, Ramírez AM, Raimann JG, Pérez-Grovas H. Association of intradialytic hypotension and convective volume in hemodiafiltration: results from a retrospective cohort study. BMC Nephrol. 2012;13:106.
64. Santoro A, Mancini E, Canova C, Mambelli E. Thermal balance in convective therapies. Nephrol Dial Transplant. 2003;18 Suppl 7:vii41–5.
65. Canaud B, Bowry SK. Revisiting frontiers of tolerability and efficacy in renal replacement therapy. Am J Kidney Dis. 2014;64:171–3.
66. Karamperis N, Sloth E, Jensen JD. Predilution hemodiafiltration displays no hemodynamic advantage over low-flux hemodialysis under matched conditions. Kidney Int. 2005;67: 1601–8.
67. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol. 1998;9(12 Suppl):S16–23.
68. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR. Assessment and management of hypertension in patients on dialysis. J Am Soc Nephrol. 2014;25:1630–46.
69. Briet M, Boutouyrie P, Laurent S, London GM. Arterial stiffness and pulse pressure in CKD and ESRD. Kidney Int. 2012;82:388–400.
70. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. J Am Soc Nephrol. 2001;12:1079–84.
71. Beerenhout CH, Luik AJ, Jeuken-Mertens SG, Bekers O, Menheere P, Hover L, Klaassen L, van der Sande FM, Cheriex EC, Meert N, Leunissen KM, Kooman JP. Pre-dilution on-line haemofiltration vs low-flux haemodialysis: a randomized prospective study. Nephrol Dial Transplant. 2005;20:1155–63.
72. Quellhorst E, Schuenemann B, Doht B. Treatment of severe hypertension in chronic renal failure by haemofiltration. Proc Eur Dial Transplant Assoc. 1977;14:129–35.
73. Mostovaya IM, Bots ML, van den Dorpel MA, Grooteman MP, Kamp O, Levesque R, Ter Wee PM, Nubé MJ, Blankestijn PJ. A randomized trial of hemodiafiltration and change in cardiovascular parameters. Clin J Am Soc Nephrol. 2014;9:520–6.

74. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, Hur E, Demirci MS, Demirci C, Duman S, Basci A, Adam SM, Isik IO, Zengin M, Suleymanlar G, Yilmaz ME, Ozkahya M, Turkish Online Haemodiafiltration Study. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28:192–202.
75. Charitaki E, Davenport A. Does hemodiafiltration reduce vascular stiffness measured by aortic pulse wave velocity compared with high-flux hemodialysis? Hemodial Int. 2014;18:391–5.
76. Georgianos PI, Sarafidis PA, Karpetas A, Kosmidis D, Sioulis A, Liakopoulos V, Stamatiadis DN, Papagianni A, Zebekakis PE, Nikolaidis P, Lasaridis AN. Hemodiafiltration does not have additional benefits over hemodialysis on arterial stiffness, wave reflections and central aortic pressures. Blood Purif. 2014;37:18–26.
77. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, den Hoedt CH, van der Tweel I, Lévesque R, Nubé MJ, ter Wee PM, Blankestijn PJ, CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.

Chapter 18
Nutritional Aspects of On-Line Hemodiafiltration

Pieter M. ter Wee and Denis Fouque

Abstract As renal function deteriorates, worsening of appetite and a decline in the nutritional state is frequently observed in patients with chronic kidney disease (CKD). The term Protein Energy Wasting (PEW) describes a state of decreased body protein and energy stores. PEW is defined as the presence of three out of the following four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake. Besides inflammation, oxidative stress and an altered metabolic and hormonal balance, retention of middle molecular weight (MMW) and protein bound uremic toxins may contribute to the decreased appetite and poor nutritional state in patients with CKD, especially when treated by hemodialysis (HD). In these patients, blood levels of phosphate, which is considered a uremic toxin, are considerably elevated. Of interest, its control in online post dilution HDF is markedly better than in low-flux HD, but comparable to high-flux HD. In HD, loss of amino-acids occurs concomitantly with proteolysis of body stores. As a result, blood levels of amino-acids remain unaltered at the cost of muscle catabolism. As of yet, major differences are not observed between patients who are treated with HD or HDF. Future studies are needed to resolve the question whether treatment with high volume HDF will alleviate PEW in our patients.

Keywords Nutrition • Protein energy wasting • Oxidative stress • Phosphate • Muscle catabolism • Amino acids • Albumin • Appetite

P.M. ter Wee, MD, PhD
Department of Nephrology, VU University Medical Center and ICaR-VU, Amsterdam, The Netherlands

D. Fouque, MD, PhD (✉)
Department of Nephrology Nutrition Dialysis, Centre Hospitalier Lyon Sud, Chemin du Grand Revoyet, Pierre Bénite 69495, France
e-mail: denis.fouque@chu-lyon.fr

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_18

Introduction

Chronic kidney disease (CKD) is associated with metabolic derangements and late complications, including a substantially increased risk of all-cause and cardiovascular morbidity and mortality, especially in dialysis patients. Since the increased risk on an adverse clinical outcome is still significant after correction for traditional risk factors such as age, smoking, hypertension, diabetes and lipid abnormalities, other factors may contribute as well. One of these factors is protein energy wasting (PEW), which has been defined as abnormalities in at least three out of four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake [1].

Thus, insufficient intake of nutrients is one of the factors contributing to PEW. Patients with CKD frequently have loss of appetite, which increases in severity during the course of the disease and is worst in dialysis patients [2]. After the start of renal replacement therapy, appetite usually improves, but with ongoing time it drops again progressively. Similarly, as demonstrated by Ikizler et al. [3], spontaneous protein intake decreases in patients with advancing GFR loss, which clearly contributes to the risk of developing PEW and frailty. Although the exact reasons for the loss of appetite and decreased protein intake are at present unknown, it is generally assumed that accumulation of toxic uremic substances is at least partially responsible for these observations. As uremic retention products, especially those in the middle molecular weight (MMW) range, are better removed by (on-line) hemodiafiltration (HDF) as compared to standard HD [4], treatment with HDF may improve the nutritional state in patients with end-stage-renal disease (ESRD).

Hemodiafiltration and Phosphate Removal

Serum phosphate, which is actually a low molecular weight substance, behaves like a MMW compound as it is surrounded by water molecules that makes it water soluble. Indeed, it could be demonstrated that HDF results in a higher clearance of phosphate than standard HD, possibly due to mobilization from a deep compartment induced by the high intradialytical removal of this solute [5]. Comparable results were obtained in a large recent randomized prospective trial (RCT) comparing post-dilution on-line HDF with low-flux HD three times a week HD [6]. In this study, the drop in phosphate could not be explained by changes in the prescribed medication, as the amount of non-calcium containing phosphate binders remained unchanged or tended to decline in HDF patients and increased in individuals treated with HD. Assuming that dietary intake had not changed over time in either group, this observation could indeed be explained by better phosphate removal during on-line HDF. This was confirmed in a recent meta-analysis [7]. Thus, increased phosphate removal could not only contribute to a better phosphate control, but potentially

also to an increased dietary protein intake, a better clinical outcome and a reduced amount of unpalatable phosphate binders. In this respect, it should be mentioned however, that two other large recent RCTS comparing HDF with high-flux HD did not show marked differences in phosphate levels between treatment arms, despite the achievement of high convection volumes in the latter [8, 9].

Hemodiafiltration and Protein Losses

It has been long known that standard HD per se results in a substantial loss of amino acids [10]. Subsequently, Deleaval et al. [11] demonstrated that serum levels of amino acids especially dropped during the first hour of HD and remained constant during the following 3 h. Since it was previously shown that treatment with HD induces proteolysis of body proteins [12], the same authors concluded that the fall in amino acid levels during the part of HD is counterbalanced by substitution from proteolysed proteins, resulting in a stabilizing of blood amino acid levels during the last part of the session [11]. Thus, HD per se might contribute to PEW in at least two ways, first through the loss of amino acids from the blood into the dialysate and second through muscle and whole body protein catabolism during treatment. Similar conclusions may hold true for HDF, as with this technique losses of essential and non-essential amino acids have been reported as well, although a direct comparison between intermittent HDF and standard HD techniques is lacking [13]. Since, however, a lower inflammatory response has been described during HDF than during HD [14, 15], which could result in less catabolism, the long-term outcome of HDF treatment on nutritional status is unclear upfront.

Hemodiafiltration and Nutritional State

In 2005 Bossola et al. [16] reported on a single center experience in which they prospectively followed eight patients for 8 months after switching them from thrice weekly intermittent HD to HDF with on-line regeneration of ultrafiltrate. After 12 months no changes in nutritional parameters were seen, although the malnutrition inflammation score (MIS) tended to improve. In 2006 the results of a 4-years prospective observational study on 31 subjects treated with on-line HDF were reported [17]. Significant changes in normalized protein catabolic rate, albumin, prealbumin, transferrin and creatinine, however, were not observed. By contrast, body mass index, fatty mass and free fatty mass improved in 12 patients after 6 months of treatment with predilution on-line HDF [18]. Likewise, it was demonstrated in a prospective single center study that 3 years of treatment with on-line HDF resulted in an improved appetite and overall well-being, which was associated with increases in dry weight, body mass index and normalized protein nitrogen appearance [19]. In a large cohort study, Vilar et al. [20] showed that

after a 5 year observation period 232 patients treated with on-line HDF had a 0.66 hazard for death compared to 626 patients treated with high-flux HD. Despite these promising findings, however, difference in nutritional status between the groups could not be found. In 15 children who had been treated with growth hormone but still were growth retarded, switching from standard thrice weekly HD to daily predilution on-line HDF for an average period of 20.5 months resulted in catch up growth and a rise in body mass, which was attributed by the investigators to less malnutrition and less cachexia [21]. In a cross over study in 24 patients treated with conventional bicarbonate HD, Matsuyama et al. [22] found that on-line HDF with acetate-free bicarbonate dialysis fluid improved leptin and neuropeptide Y levels together with lower levels of interleukin 6 and C-reactive protein, and a trend towards a higher protein catabolic rate (PCR), which is considered a reliable measure of protein take. From these observations the authors suggested that on-line HDF with acetate-free bicarbonate resulted in a decrease in microinflammation and an improved nutritional status. In 22 patients who were switched from thrice weekly daytime on-line HDF to nocturnal every-other-day on-line HDF for 1 year, a rise in dry body weight was observed, although other markers of nutritional status like normalized PCR (nPCR), albumin and prealbumin did not change [23]. In contrast to the above mentioned results, Orasan et al. [24] recently showed in 44 patients that after switching from standard HD to on-line HDF, both serum albumin levels and nPCR were significantly lower during the HDF period, while body mass index tended to decrease. In a large multi-center RCT (the CONvective TRAnsport Study; CONTRAST), in which 714 dialysis patients were randomized to either low-flux HD or on-line post dilution HDF, both serum albumin and body mass index decreased significantly over time [15], without differences between patient groups. At present results on all-cause mortality of two other large prospective RCTs comparing HD and HDF have been reported, but so far data on nutritional aspects of those studies is limited. Time averaged serum albumin was slightly lower in the HDF group of the Turkish study (3.93 ± 0.24 vs 3.99 ± 0.27 g/dL, $p < 0.001$) [8]. In the ESHOL study there was a slight but significant trend for albumin and dry body weight to decrease in the HDF group as well [9].

Summary and Conclusions

In summary, from the currently available literature it can be concluded that there are no convincing data demonstrating that on-line HDF leads to improvements in the nutritional status of ESRD patients. Although some benefits have been described in observational studies, differences between groups were not found in a large RCT comparing on-line HDF with conventional HD [15]. While most studies showed either no change or some beneficial effects, so far in only one study a negative influence of on-line HDF on nutritional outcome was reported. The disadvantage of an increased loss of nutrients and vitamins, as may occur in high volume HDF, should

be weighed against benefits on inflammatory status, appetite and (less) protein catabolism. Altogether it can be concluded that more research is warranted to finally conclude what the impact of on-line HDF specifically has on the nutritional state of ESRD patients.

Teaching Points

- As renal failure deteriorates, worsening of appetite and nutritional state is frequently observed
- Protein energy wasting (PEW) is defined as the presence of three out of the following four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake.
- Besides inflammation and other contributory factors, accumulation of MMW uremic toxins may contribute to the poor appetite and nutritional state in patients with CKD
- Phosphate control in online post dilution HDF is markedly better than in low flux HD, but comparable to high-flux HD.
- Loss of amino-acids during HDF does not seem much different than during high flux HD
- In ESRD patients, the nutritional state worsens over time, irrespective of the dialysis modality applied

References

1. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
2. Carrero JJ. Identification of patients with eating disorders: clinical and biochemical signs of appetite loss in dialysis patients. J Ren Nutr. 2009;19:10–5.
3. Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM. Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol. 1995;6:1386–91.
4. Wizemann V, Kulz M, Techert F, Nederlof B. Efficacy of haemodiafiltration. Nephrol Dial Transplant. 2001;16 Suppl 4:27–30.
5. Minutolo R, Bellizzi V, Cioffi M, Iodice C, Giannattasio P, Andreucci M, et al. Postdialytic rebound of serum phosphorus: pathogenetic and clinical insights. J Am Soc Nephrol. 2002;13:1046–54.
6. Penne EL, van der Weerd NC, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55:77–87.
7. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2013;28:2859–74.
8. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28:192–202.

9. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
10. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. Kidney Int. 1994;46:830–7.
11. Deleaval P, Teta D, Vianey-Saban C, Claustrat B, Kopple JD, Fouque D. Early drop and plateau plasma amino-acid pattern during hemodialysis (HD) session. J Am Soc Nephrol. 2007;18:482A.
12. Ikizler TA, Pupim LB, Brouillette JR, Levenhagen DK, Farmer K, Hakim RM, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. Am J Physiol Endocrinol Metab. 2002;282:E107–16.
13. Ragazzoni E, Carpani P, Agliata S, CCiranna G, Cusinato S, et al. HFR vs HDF-on line: plasmatic amino acid loss evaluation. G Ital Nephrol. 2004;21 Suppl 30:S85–90.
14. Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. Nephrol Dial Transplant. 2013;28:438–46.
15. Den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Penne EL, Mazairac AH, et al. Clinical predictors of decline in nutritional parameters over time in ESRD. Clin J Am Soc Nephrol. 2014;9:318–25.
16. Bossola M, Muscaritoli M, Tazza L, Giungi S, Panocchia N, Rossi FF, et al. Switch from bicarbonate hemodialysis to hemodiafiltration with online regeneration of the ultrafiltrate (HFR): effects on nutritional status, microinflammation, and beta-microglobulin. Artif Organs. 2005;29:259–63.
17. Munoz R, Gallardo I, Valladares E, Saracho R, Martinez I, Ocharan J, et al. Online hemodiafiltration: 4 years of clinical experience. Hemodial Int. 2006;10 Suppl 1:S28–32.
18. Savica V, Ciolino F, Monardo P, Mallamace A, Savica R, Santoro D, et al. Nutritional status in hemodialysis patients: options for on-line convective treatment. J Ren Nutr. 2006;16:237–40.
19. Tiranathanagul K, Praditpornsilpa K, Katavetin P, Srisawat N, Townamchai N, Susantitaphong P, et al. On-line hemodiafiltration in Southeast Asia: a three-year prospective study of a single center. Ther Apher Dial. 2009;13:56–62.
20. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009;4:1944–53.
21. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25:867–73.
22. Matsuyama K, Tomo T, Kadota J. Acetate-free blood purification can impact improved nutritional status in hemodialysis patients. J Artif Organs. 2011;14:112–9.
23. Maduell F, Arias M, Duran CE, Vera M, Fontsere N, Azqueta M, et al. Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative. Nephrol Dial Transplant. 2012;27:1619–31.
24. Orasan RA, Patiu IM, Anghel D, Bejan C, Iosub L, Totolici C, et al. Variation of clinical and laboratory features in chronic dialysis patients treated with high-flux hemodialysis after switching to online hemodiafiltration. Int Urol Nephrol. 2013;45:1415–22.

Chapter 19
Why Is High Volume Online Post-dilution Hemodiafiltration Associated with Improved Survival?

Menso J. Nubé

Abstract Retention of middle molecular weight (MMW) uremic toxins has been related to mortality in patients with end-stage kidney disease (ESKD). Therefore, interest has shifted from pure diffusive dialysis techniques, such as low-flux hemodialysis (HD), which remove only small water solutes, towards convective therapies, such as hemodiafiltration (HDF), which remove larger compounds as well. Controversy exists, however, as to whether the positive effect of HDF on MMW solutes translates in a superior clinical outcome. Here, we describe the results of three recent large randomized controlled trials (RCT), comparing online post-dilution HDF with HD, and four systematic reviews on convective therapy, and discuss the discrepancies between these studies. Actually, it appears that the concept of 'convective therapy' is confusing, as it is not strictly defined and differently interpreted. When convection volumes >21 L/session are applied, especially cardiovascular (CV) mortality is markedly reduced, while the incidence non-CV death due to infections or malignancies, remains unaltered. Echocardiographic analysis suggests that left ventricular (LV) function and structure worsen in HD and remain stable in HDF. Moreover, intradialytic hemodynamic stability appears better preserved during HDF. Currently, there is no convincing evidence that HDF lowers CV mortality by improvements in inflammation, nutrition, CKD-mineral and bone disease, dyslipidemia and anemia control.

Keywords Hemodialysis • Hemodiafiltration • Survival • Mortality • Hemodynamic stability • Mechanisms • Non-cardiovascular mortality • Convection volume • Pathophysiology • Heparin • Uremic toxins

M.J. Nubé, MD, PhD
Department of Nephrology, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081 HV, The Netherlands
e-mail: mensonube@gmail.com

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_19

Introduction

HD is the standard renal replacement therapy for patients with ESKD. Despite major technological improvements over the last decades, however, overall survival remains poor. Standard HD with low permeable membranes has shown to be an effective treatment for removing small water soluble substances, such as urea by diffusion, but simply increasing urea clearance did not improve survival [1]. To remove MMW uremic toxins more efficiently, high permeable dialyzers were introduced, which however, also did not reduce mortality [1, 2]. To enhance the clearance of MMW, HDF was developed, which combines diffusive transport of small molecules with an effective removal of larger solutes by convection. In modern HDF, fluid balance is maintained by the administration of *online* prepared ultrapure substitution fluid which can be infused before (predilution), midway (middilution) and after (postdilution) the dialyzer. As the majority of recent clinical studies is performed in the postdilution mode, this overview deals particularly with this type of treatment. Currently, controversy exists as to whether the positive effect of HDF on MMW solutes translates into a superior clinical outcome. In addition, the amount of convection required to obtain optimal benefit, is unknown [3]. In the present chapter, a summary is given of current literature on all-cause, CV and non-CV mortality, and a possible dose-response effect. In addition, potential mechanisms behind the beneficial effects of high volume HDF on survival are discussed.

Clinical Aspects: Overall and Cardiovascular Mortality

Recently, three large RCTs, comparing *online* post-dilution HDF with HD, were published [4–6]. While the Dutch CONTRAST and the Turkish HDF Study (THDFS) showed no differences in clinical outcome between treatment arms, in the Spanish ESHOL study a favorable effect of HDF on overall survival was found (Table 19.1). Both ESHOL and THDFS showed a lower, but non-significant, incidence in cardiovascular events in HDF patients.

Table 19.1 All cause and cardiovascular mortality in the three major RCTs on postdilution online hemodiafiltration

	CONTRAST (n = 714)	THDFS (n = 782)	ESHOL (n = 906)
	HDF versus lowflux HD	HDF versus highflux HD	HDF versus highflux HD
Overall	0.95 (0.75–1.20)	0.79 (0.55–1.14)	0.70 (0.53–0.92)
Cardiovascular	0.80 (0.52–1.24)	0.72 (0.45–1.13)	0.67 (0.44–1.02)

Hazard ratio for mortality and cardiovascular mortality with 95 % confidence limits, in the three major RCTs on postdilution online HDF
HDF hemodiafiltration, *HD* hemodialysis, *CONTRAST* [4] CONvective TRAnsport STudy, *THDFS* [6] Turkish HDF Study, *ESHOL* [5] Estudio de Supervicencia de Hemodiafiltracion OnLine

To further answer the question whether dialysis treatment with 'convective therapies' improves clinical outcome, in the last 2 years four large meta-analyses have been published, which, however, showed a discordant outcome [7–10]. Yet, as discussed more extensively in Chap. 16, it appeared that these analyses differ in the number of studies and patients included, the definitions of comparator and intervention therapy, and type of studies, varying from small observational to large prospective RCTs.

In one meta-analysis low-flux HD was the reference therapy [9], while both low-flux and high-flux HD were reference therapies in three others [7, 8, 10]. Considering the intervention arm, inclusion covered different combinations of high-flux HD, *off-line* HDF, hemofiltration (HF), acetate-free biofiltration (AFB) and on-line postdilution HDF. Some of these modalities, however, can hardly be considered modern convective therapies, as convection volumes of 10–12 L/session are similar to the amount of internal filtration in high-flux HD and completely different from high volume HDF (>21 L/session) [11]. In our opinion, a statement on today's convective therapies should be based on a convection volume of at least 17–19 L/session in the postdilution mode [12]. The only meta-analysis which largely fulfills this criterion clearly shows an all cause and CV survival advantage of HDF over HD [7]. Interestingly, after removing AFB and *off-line* HDF from the meta-analysis by Nistor et al. [8], all cause mortality was superior in HDF patients [RR 0.82 (95 % CI 0.72–0.93)], Table 19.2 [12].

The latter findings were confirmed in an individual participant data meta-analysis (IPD), using data from CONTRAST, ESHOL, THDFS and a fourth not yet published French HDF study. Recent data indicate that HDF reduces the risk of all-cause mortality by 14 % (HR 0.86 [95 % CI 0.75–0.99]) and cardiovascular mortality by 23 % (HR 0.77 [95 % CI 0.61–0.97]) [4–6, 13].

Causes of Cardiovascular Death in HD and HDF

As shown by the meta-analysis by Mostovaya et al. [7], CV mortality is reduced by 27 %, and perhaps even further (55 %) when high volumes are applied.[5] In theory, both a decrease in the incidence in heart failure, which is difficult to

Table 19.2 All cause and cardiovascular mortality in meta-analysis on convective therapies

	Studies[a]	Participantsb	All cause mortality	Cardiovascular mortality
Nistor [8]	11/6	3396/2889	0.87 (0.70–1.07)	0.75 (0.58–0.97)
Nistor (without AFB and *offline* HDF) [12]			0.82 (0.72–0.93)	na
Susantitaphong [9]	21/3	4766/3207	0.88 (0.76–1.02)	0.84 (0.71–0.98)
Mostovaya [7]	6/3	2885/2402	0.84 (0.73–0.96)	0.73 (0.57–0.92)
Wang [10]	10/4	2998/2478	0.83 (0.65–1.05)	0.85 (0.66–1.10)

Relative risk for mortality and cardiovascular mortality with 95 % confidence limits

[a]Before/: number of studies used for calculations on all cause mortality, after/: number of studies used for calculations on cardiovascular mortality

[b]Before/: participants in studies on all cause mortality, after/: participants in studies on cardiovascular mortality

diagnose in ESKD, ischemic heart disease, sudden death and stroke may play a role in this respect. Interestingly, in ESHOL a reduction in stroke was found, while the incidence of heart failure and ischemic heart disease was similar [5]. None of the three recent RCTs found a difference in sudden death between HDF and HD.

Cardiovascular Abnormalities in HD and HDF

Echocardiographic analysis may provide an answer to the question whether variations in LV structure and function explain the CV survival benefit of HDF. Indeed, the scarce studies performed showed improvement or stabilization in the HDF group and cardiac worsening in HD patients [14, 15]. Interestingly, from a small RCT in incident patients it appeared that treatment with predilution HF, a pure convective therapy, was associated with a more favorable development of LV mass (LVM) than low-flux HD [16]. Analysis of a large subset of the CONTRAST cohort revealed that, whereas both LVM and ejection fraction deteriorated over time in HD patients, these parameters remained stable in the HDF group [17]. Moreover, in a small RCT it was recently shown that high volume HDF (>22 L/session) prevented the endothelial dysfunction and stiffening of conduit arteries that was observed in HD patients [18].

Relation Between Clinical Outcome and Magnitude of the Convection Volume

Post hoc analysis of all three recent RCTs suggested a positive relationship between convection volume and clinical outcome, Fig. 19.1 (see also Chap. 16). Similar findings were suggested before by DOPPS [19]. Although the optimal convection volume is unclear, a minimum of 21 L/session appears appropriate [7].

Hemodynamic Aspects

Intradialytic hypotension (IDH) is a common problem in HD, which has been related to cardiac stunning, bowel ischaemia and brain hypoperfusion. By echocardiography, during HD a compromised cardiac function was found in 65 % of the patients, which depended on the ultrafiltration rate and severity of IDH [20]. Moreover, patients with marked IDH have higher serum levels of cardiac enzymes [21] and reduced life expectancy [22]. Interestingly, treatment with cooled dialysate (CD-HD) reduced IDH, HD-induced brain injury [23] and improved CV survival [24]. In two large RCTs, blood pressure stability during HDF was superior to HD

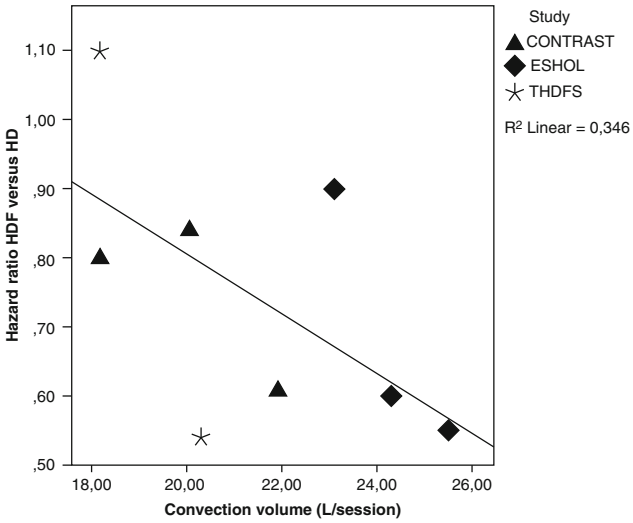


Fig. 19.1 Association between hazard ratio for mortality and convection volume in the different tertiles (or below/above the median) of convection volume in RCTs on hemodiafiltration: *CONTRAST* [4]: CONvective TRAnsport STudy, *THDFS* [6]: Turkish HDF Study, *ESHOL* [5]: Estudio de Supervicencia de Hemodiafiltracion OnLine

[5, 25] but not in a third [6]. When cool dialysate was used both in HDF and HD, hemodynamic changes, as measured by blood pressure, blood volume, cardiac output and microcirculation, did not differ [26]. Similarly, solute movements between the intra and extracellular compartments during HDF and CD-HD were similar [27]. Hence, it appears that intradialytic hemodynamic stability is better preserved during HDF than during standard HD, but analogous to CD-HD. Unfortunately, none of the recent RCTs reported dialysate temperature.

Clinical Aspects: Non-cardiovascular Mortality

Besides a high risk of CV death, ESKD patients have an elevated risk of non-CV mortality. As shown in a large study from the ERA-EDTA registry, the standardized mortality risks were equally increased, if compared to the general population (RR 8.8; 95 % CI 8.6–9.0 and RR 8.1; 95 % CI 7.9–8.3, resp.) [28]. Since the excess mortality in ESKD shows a 'normal' distribution, it is vital to know whether HDF decreases not only CV death, but also non-CV events.

Infection-Related Mortality

Infectious complications, which account for one quarter of total mortality in patients with ESKD, [29] are usually linked to bacterial spread from vascular access, particularly in case of central venous catheters (CVC). Whereas no overall difference was found in CONTRAST [30], infection-related mortality in ESHOL was lowest in HDF patients (HR 0.45, 95 % CI 0.21–0.96) [5]. Whether this outcome results from a lower CVC use in the HDF group (7 % versus HD 13 %) or from the high convection volumes applied remains to be established. Unpublished data from the IPD meta-analysis, as outlined before, showed a similar incidence of infection-related mortality (HDF HR 0.94; 95 %CI 0.66–1.30) in both treatment arms [13].

Other Causes of Death

None of the meta-analyses or RCTs reported a decline in other causes of death, such as withdrawal from dialysis [29] or malignancies. Considering this 'rest group', unpublished findings from the IPD meta-analysis showed similar mortality rates: HDF HR 0.92; 95 %CI 0.73–1.15.

Pathophysiological Aspects

Both classical risk factors, such as high blood pressure and cholesterol levels, and non-traditional risk factors, including the toxicity of uremia itself and the bio-incompatibility of the extra-corporeal system, have been implicated in the high mortality risk of ESKD.

Classical Risk Factors

Blood Pressure

From a large sub-study of CONTRAST, it appeared that mean arterial pressure (MAP) decreased over time, mainly due to a reduction in peripheral resistance. As cardiac output remained unaltered, the authors speculated that loss of functioning renal tissue ultimately leads to a reduced stimulation of the renin-angiotensin-aldosteron- and sympathic systems [17], which are overactivated in CKD [31]. Differences between the HD and HDF groups, however, were not observed. By meta-analysis, HDF treatment did not influence systolic BP, diastolic BP, MAP or prescription of anti-hypertensive drugs [8, 9]. In accordance with these findings, Georgianos et al. found that HDF did not have beneficial effects on arterial stiffness, wave reflections or central aortic pressure [32].

Dyslipidemia

Dyslipidemia is frequently observed in ESKD. Controversy exists as to whether high lipid levels contribute to the greatly elevated CV risk in these patients. Whereas HDL-C exerts potent anti-thrombotic, anti-inflammatory and anti-apoptotic effects in the general population, in CKD fundamental structural alterations of this particle have been identified [33]. Therefore, the mere measuring of lipid profiles may not reliably reflect CV risk. In short term HDF studies, confusing data were published, from higher HDL-C and lower triglyceride (TG) levels to increased LDL-C and stable TG values [34, 35]. A recent meta-analysis showed a reduction in TG and stabilization of total cholesterol and LDL-C [9]. Interpretation, however, is difficult as the mere raising of HDL and lowering of LDL does not automatically entail return of their (anti) atherogenic properties.

Other Risk Factors

Large RCTs comparing high-flux with low-flux HD suggested that besides diabetics, patients with a albumin <40 g/L and subjects with a dialysis vintage >30 months would benefit from 'convective therapy' [1, 2]. However, with the exception of a high co-morbidity index in ESHOL, none of the meta-analyses or recent large RCTs showed different effects of HDF in these and other selected subgroups, such as age and gender.

Non-traditional Risk Factors

Inflammation and Oxidative Stress

A chronic low grade inflammatory state is common in ESKD [36]. Besides uremia-related factors, such as accumulation of uremic toxins, dialysis-related factors, including the bio-incompatibility of the extracorporeal system, have been implicated in this process. HDF may decrease inflammatory activity by enhanced clearance of MMW uremic toxins; on the other hand, the infusion of large amounts of substitution fluid may aggravate the micro-inflammatory state. Whereas some observational studies reported on a decrease of inflammation and oxidative stress after treatment with convective therapies [37, 38], several small RCTs did not [39]. Comparison in observational studies is often hampered by the fact that, while in HDF ultrapure (UP) dialysis fluid (micro-organisms <0.1 CFU/ml; endotoxins <0.025 EU/ml) is mandatory, in HD the dialysis fluid is frequently consistent with 'standard quality' (<100 CFU/ml; <0.25 EU/ml) [40, 41]. Of note, use of UP fluid in HD resulted not only in a decline in markers of inflammation and oxidative stress, but also in increased serum albumin and hemoglobin levels [42]. As the same water treatment system was used in both arms of CONTRAST and ESHOL, it is unlikely that differences in clinical outcome, as observed in ESHOL and in the high volume

Table 19.3 Effect of HDF on biochemical parameters in the three major RCTs

	CONTRAST (n = 714)	THDFS (n = 782)	ESHOL (n = 906)
	HDF versus lowflux HD	HDF versus highflux HD	HDF versus highflux HD
Kt/Vurea	↑	↑	↑
B2 microglobulin	↓	↔	↓
PTH	NA	↔	↔
Phosphorus	↓	↔	↔
ESA index	↔	↓	↔
Albumin	↔[a]	↓	↔[a]
Bicarbonate	NA	↑	NA
Total cholesterol	↔	NA	↔
CRP	↔	↔	↔

The arrows indicate higher (↑) in HDF, lower (↓) in HDF, or no difference (↔) between HDF and HD. *NA* not available, *RCT* randomized controlled trial, *ESA* erythropoietin stimulating agent, *PTH* parathormon, Kt/V_{urea} K = dialyzer clearance of urea, t = dialysis time, V = urea distribution volume, *CRP* C-reactive protein

CONTRAST [4] COnvective TRansport STudy, *THDFS* [6] Turkish HDF Study, *ESHOL* [5] Estudio de Supervicencia de Hemodiafiltracion OnLine

[a]Albumin decreased equally in both groups

group of CONTRAST, result from a dissimilar quality of dialysis fluid. Moreover, CRP levels did not differ between treatment arms in either study (Table 19.3).

CKD-Mineral and Bone Disorder

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is the term used to describe a constellation of abnormalities that may lead to bone disturbances and extra-skeletal calcifications in soft tissues and arteries. Biochemically this syndrome is characterized by abnormalities in serum phosphate, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), calcium and vitamin D.

Retention of phosphate has been implicated in all cause and CV mortality [43, 44]. Phosphate levels are generally lower during treatment with convective therapies than with low-flux HD [9]. When comparing HDF with high-flux HD, results are contradictory [26, 45]. Actually, treatment of hyperphosphatemia consists of both phosphate-binding agents and dialysis. Hence, when comparing phosphate control between modalities, phosphate levels as well as the amount of phosphate-binding drugs should be taken into account. Both in CONTRAST and the PAN Thames Renal Audit, phosphate levels were lower in HDF than in HD patients treated with low-flux dialyzers [46, 47]. By contrast, neither in THDFS nor in ESHOL differences were observed between (high-flux) HD and HDF (Table 19.3) [5, 6].

Phosphate is excreted by the kidney in response to PTH (9.5 kD) and FGF23 (see below). High serum PTH levels in ESKD have been related to a poor clinical outcome [48], although suppression by cinacalcet did not reduce mortality [49]. In

THDFS as well in ESHOL, PTH levels were similar in both treatment arms (Table 19.3). Of note, previously it was shown that PTH levels decrease after a session with low volume HDF, but increase after high volume HDF, possible as a result of a negative calcium balance [50]. In a meta-analysis comparing convective therapies with low-flux HD, differences between treatment strategies were not found [9].

Both human and animal data suggest that an increased FGF23 (32 kD) value is the earliest detectable biochemical alteration in CKD-MBD [51]. Levels of this phosphatonin, which is produced by bone marrow cells, are 100–1000-fold higher in ESKD than in healthy individuals. While no intra-dialytical changes were observed during low-flux HD [52], FGF23 removal was markedly higher during HDF than during high-flux HD [26, 53]. As FGF23 has been related to LVH [54] and CV events, especially congestive heart failure [55, 56], reduction by HDF may lower CV mortality in ESKD.

Other Conditions Which Have Been Related to Mortality in ESKD

Worsening of the nutritional state is a well known feature in ESKD. The term Protein Energy Wasting (PEW) describes a state of decreased body stores of protein and energy fuels [57]. Various score systems have been applied to measure PEW, such as the Subjective Global Assessment (SGA), Malnutrition Inflammation Score (MIS), Geriatric Nutritional Risk Index (GNRI) and the composite Protein Energy Nutrition Score (cPENS) [58]. Recent observations from CONTRAST indicate that SGA and MIS predict mortality no better than a single albumin measurement [58, 59]. While in the THDFS, time averaged albumin levels were lower in HDF patients, both in ESHOL and CONTRAST albumin levels decreased over time, without differences between groups (Table 19.3) [5, 60].

Anemia is a hallmark of ESKD. Besides a reduced production of erythropoietin (EPO) and EPO resistance, a diminished enteric uptake of iron and a shortened lifespan of red blood cells may play a role. EPO resistance has been associated with (functional) iron deficiency, impaired nutritional state, chronic micro-inflammation and retention of MMW solutes. As for the latter, it was suggested that convective treatment would improve EPO resistance and hence anemia [61]. Against expectations, however, a large RCT did not show any advantage of HDF [62]. Moreover, in CONTRAST, ESHOL and THDFS, neither Hb values, nor transferrin saturation index or ferritin levels differed between groups (Table 19.3) [5, 6, 63]. With respect to the EPO resistance index in HDF patients, contradictory results were obtained, being lower in THDFS, and similar in ESHOL and CONTRAST. In a sub-analysis of CONTRAST, EPO resistance did not differ between low (<18 L) and high (>22 L) volume HDF [63].

Accumulating evidence indicates that mild acidosis in ESKD is related to an adverse clinical outcome. Correction has been positively associated with SGA, residual renal function and normalized protein appearance rate [64], shorter

hospitalization and lower mortality [65]. In a cross-over study, net bicarbonate gain was slightly higher during HDF, while at the end of the session acid-base status was similar to HD [66]. In THDFS, a positive trend was observed between bicarbonate levels and convection volume (Table 19.3) [6]. Hence, although not yet convincingly demonstrated, a better correction of acidosis during HDF may contribute to the improved survival in this patient group.

Treatment-Related Aspects

Platelet Activation and (Anti)coagulation

In HD, unfractionated heparin or low-molecular-weight heparin (LMWH) is administered to prevent clotting. During HDF, however, the intra-dialyzer transmembrane pressure is considerable higher and, due to the high ultrafiltration rate, blood viscosity increased [67]. Consequently, platelet activation and coagulation are more pronounced. Indeed, in THDFS the heparin dose was 25 % higher in HDF than in HD patients, while in CONTRAST the LMWH dose was 10 % higher [6, 68]. Currently, however, it is unknown whether increased platelet activation and coagulation at the one hand and use of additional heparin or LMWH on the other is beneficial or harmful to the patients. The use of relatively high doses, three times per week, year after year, may reduce CV events in subjects with a high cardiovascular risk profile. In addition, malfunctioning and chronic depleted platelets, as demonstrated before in HD patients [67, 69], may protect against vascular disease [70]. Alternatively, it is conceivable that these side effects of HDF actually harm the patients.

Clearance of Low-Molecular Weight, Middle-Sized and Protein-Bound Solutes

Uremic solutes are generally subdivided in three major classes: (1) water soluble compounds (<500 Da), which are easily removed by any dialysis strategy, (2) MMW substances (0.5–40 kD), which can only be removed by convection, and (3) protein-bound uremic toxins, which are difficult to remove [71]. With respect to the adequacy parameter Kt/V_{urea}, a measure of small water soluble molecule clearance, all three recent RCTs showed an improvement in HDF patients (Table 19.3), while mortality was only reduced in ESHOL [4–6]. Considering MMW solutes, high beta-2-microglobulin (β2M) levels have been shown to be independently associated with overall and CV mortality [72]. However, while in CONTRAST and ESHOL β2M levels were lower in HDF than in HD patients, only ESHOL showed a benefit of HDF (Table 19.3). Multiple toxic effects have been attributed to protein-bound

phenolic compounds, such as p-cresylsulfate. P-cresol is generated by intestinal bacteria and conjugated to p-cresylsulfate and p-cresylglucuronide. In-vitro these compounds induce toxic effects on endothelial integrity and leucocyte rolling [73]. Clinically, these substances have been associated with an adverse CV outcome [71]. Whereas high-flux HD did not augment the reduction of protein-bound toxins, addition of convective transport by HDF improved the removal of these compounds slightly [74].

Summary and Conclusions

Is Online Post-Dilution HDF Associated with an Improved Survival?

From this overview it appears first, that all-cause mortality is significantly reduced by HDF, CV events almost exclusively accounting for this beneficial effect. Other causes of mortality, such as infections and sudden death, are not different between HDF and HD. Second, it remains unclear whether the reduction in CV mortality is caused by a decline in stroke, heart failure or ischemic heart disease. Third, a convection volume of at least 21 L/session appears required for the desired effect.

Why Is High Volume HDF Associated with Improved Survival?

Having illustrated that high volume HDF is related to an improved CV survival, what are the underlying mechanisms? Are the aforementioned RCTs confounded by a favorable clinical profile of HDF patients beforehand? Although this option was not discussed in this chapter and cannot completely be ruled out, it should be mentioned that extensive corrections were made in all RCTs. Moreover, we recently showed that centre policy, rather than patient factors, determine the magnitude of the convection volume [75]. Indeed, recent data from a large prospective observational study indicate that at least 21 L of substitution fluid is feasible in more than 80 % of ESKD patients [76]. As published in individual RCTs and by meta-analysis, predialysis blood pressure was not different between groups, but HDF may improve intra-dialytic hemodynamic stability. Analysis by echocardiography indicated that the functional and structural deterioration of the LV over time in HD patients was mitigated or even absent in HDF. Convincing arguments are not available that HDF reduces CV mortality by improvements in traditional or non-traditional risk factors. With respect to solute removal, neither Kt/V_{urea} nor β2M was related to survival. By contrast, FGF23 appears a promising candidate toxin for the HDF-induced benefit on survival. Whether high doses of heparin or better correction of acidosis adds to the reduced mortality in HDF is a matter for future research.

Teaching Points

- High volume online post-dilution HDF is associated with improved overall survival
- This advantage results entirely from a lower cardiovascular mortality, possibly due to better preservation of left ventricular mass and function
- High volume online post-dilution HDF offers no benefits in terms of non-cardiovascular mortality
- The beneficial effect of high volume online post-dilution HDF on survival is not restricted to selected subgroups, such as age, co-morbidity or dialysis-vintage
- Both removal of MMW uremic toxins and improved intra-dialytical blood pressure stability may contribute to the beneficial effect of high volume online post-dilution HDF on survival
- There is no compelling evidence that high volume online post-dilution HDF reduces mortality by improvements in traditional and non-traditional risk factors
- The middle molecular weight molecule FGF23 and the protein-bound solutes p-cresyl sulfate and indoxyl sulfate are putative uremic toxins that are removed by high volume online post-dilution HDF and may explain part of its survival benefit

References

1. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347(25):2010–9.
2. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, et al. Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol. 2009;20(3):645–54.
3. Farrington K, Davenport A. The ESHOL study: hemodiafiltration improves survival-but how? Kidney Int. 2013;83(6):979–81.
4. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.
5. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
6. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
7. Mostovaya IM, Blankestijn PJ, Bots ML, Covic A, Davenport A, Grooteman MP, et al. Clinical evidence on hemodiafiltration: a systematic review and a meta-analysis. Semin Dial. 2014;27(2):119–27.
8. Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, et al. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. Am J Kidney Dis. 2014;63(6):954–67.

9. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2013;28(11):2859–74.
10. Wang AY, Ninomiya T, Al-Kahwa A, Perkovic V, Gallagher MP, Hawley C, et al. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. Am J Kidney Dis. 2014;63(6):968–78.
11. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58(2):809–17.
12. Grooteman MP, Blankestijn PJ, Nube MJ. Not all convective dialysis therapies are equal. Am J Kidney Dis. 2014;64(5):819–20.
13. Peters SAE, Bots ML, Canaud B, Davenport A, Grooteman MPC, Kircelli F, et al. Haemodiafiltration and mortality in end stage kidney disease patients. A pooled individual participant data meta-analysis from four randomised controlled trials. Nephrol Dial Transplant. 2015. doi:10.1093/ndt/gfv349.
14. Czifra A, Pall A, Kulcsar J, Barta K, Kertesz A, Paragh G, et al. Hemodialysis and hemodiafiltration differently modulate left ventricular diastolic function. BMC Nephrol. 2013;14:76.
15. Ohtake T, Oka M, Ishioka K, Honda K, Mochida Y, Maesato K, et al. Cardiovascular protective effects of on-line hemodiafiltration: comparison with conventional hemodialysis. Ther Apher Dial. 2012;16(2):181–8.
16. Alvestrand A, Ledebo I, Hagerman I, Wingren K, Mattsson E, Qureshi AR, et al. Left ventricular hypertrophy in incident dialysis patients randomized to treatment with hemofiltration or hemodialysis: results from the ProFil study. Blood Purif. 2011;32(1):21–9.
17. Mostovaya IM, Bots ML, van den Dorpel MA, Grooteman MP, Kamp O, Levesque R, et al. A randomized trial of hemodiafiltration and change in cardiovascular parameters. Clin J Am Soc Nephrol. 2014;9(3):520–6.
18. Bellien J, Freguin-Bouilland C, Joannides R, Hanoy M, Remy-Jouet I, Monteil C, et al. High-efficiency on-line haemodiafiltration improves conduit artery endothelial function compared with high-flux haemodialysis in end-stage renal disease patients. Nephrol Dial Transplant. 2014;29(2):414–22.
19. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int. 2006;69(11):2087–93.
20. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4(5):914–20.
21. Hung SY, Hung YM, Fang HC, Yeh JH, Hung GC, Wu CJ, et al. Cardiac troponin I and creatine kinase isoenzyme MB in patients with intradialytic hypotension. Blood Purif. 2004;22(4):338–43.
22. Iseki K, Shoji T, Nakai S, Watanabe Y, Akiba T, Tsubakihara Y. Higher survival rates of chronic hemodialysis patients on anti-hypertensive drugs. Nephron Clin Pract. 2009;113(3):c183–90.
23. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. J Am Soc Nephrol. 2015;26(4):957–65.
24. Hsu HJ, Yen CH, Hsu KH, Lee CC, Chang SJ, Wu IW, et al. Association between cold dialysis and cardiovascular survival in hemodialysis patients. Nephrol Dial Transplant. 2012;27(6):2457–64.
25. Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA, et al. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol. 2010;21(10):1798–807.
26. Cornelis T, van der Sande FM, Eloot S, Cardinaels E, Bekers O, Damoiseaux J, et al. Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. Am J Kidney Dis. 2014;64(2):247–56.
27. Kumar S, Khosravi M, Massart A, Potluri M, Davenport A. Haemodiafiltration results in similar changes in intracellular water and extracellular water compared to cooled haemodialysis. Am J Nephrol. 2013;37(4):320–4.

28. de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA. 2009;302(16): 1782–9.
29. den Hoedt CH, Bots ML, Grooteman MP, Mazairac AH, Penne EL, van der Weerd NC, et al. Should we still focus that much on cardiovascular mortality in end stage renal disease patients? The CONvective TRAnsport STudy. PLoS One. 2013;8(4):e61155.
30. den Hoedt CH, Grooteman MP, Bots ML, Blankestijn PJ, van der Tweel I, van den Weerd NC, et al. The effect of HDF on infections: results from the CONvective TRAnsport STudy. PLoSone 2015;10(8):e0135908.
31. Blankestijn PJ, Ligtenberg G, Klein IH, Koomans HA. Sympathetic overactivity in renal failure controlled by ACE inhibition: clinical significance. Nephrol Dial Transplant. 2000; 15(6):755–8.
32. Georgianos PI, Sarafidis PA, Karpetas A, Kosmidis D, Sioulis A, Liakopoulos V, et al. Hemodiafiltration does not have additional benefits over hemodialysis on arterial stiffness, wave reflections and central aortic pressures. Blood Purif. 2014;37(1):18–26.
33. Speer T, Zewinger S, Fliser D. Uraemic dyslipidaemia revisited: role of high-density lipoprotein. Nephrol Dial Transplant. 2013;28(10):2456–63.
34. Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, et al. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. Nephrol Dial Transplant. 2008;23(7):2337–43.
35. Vaslaki L, Major L, Berta K, Karatson A, Misz M, Pethoe F, et al. On-line haemodiafiltration versus haemodialysis: stable haematocrit with less erythropoietin and improvement of other relevant blood parameters. Blood Purif. 2006;24(2):163–73.
36. Yao Q, Lindholm B, Stenvinkel P. Inflammation as a cause of malnutrition, atherosclerotic cardiovascular disease, and poor outcome in hemodialysis patients. Hemodial Int. 2004;8(2): 118–29.
37. Calo LA, Naso A, Carraro G, Wratten ML, Pagnin E, Bertipaglia L, et al. Effect of haemodiafiltration with online regeneration of ultrafiltrate on oxidative stress in dialysis patients. Nephrol Dial Transplant. 2007;22(5):1413–9.
38. Filiopoulos V, Hadjiyannakos D, Metaxaki P, Sideris V, Takouli L, Anogiati A, et al. Inflammation and oxidative stress in patients on hemodiafiltration. Am J Nephrol. 2008;28(6): 949–57.
39. Leurs P, Lindholm B, Stenvinkel P. Effects of hemodiafiltration on uremic inflammation. Blood Purif. 2013;35 Suppl 1:11–7.
40. Akoglu H, Dede F, Piskinpasa S, Falay MY, Odabas AR. Impact of low- or high-flux haemodialysis and online haemodiafiltration on inflammatory markers and lipid profile in chronic haemodialysis patients. Blood Purif. 2013;35(4):258–64.
41. den Hoedt CH, Mazairac AH, van den Dorpel MA, Grooteman MP, Blankestijn PJ. Effect of hemodiafiltration on mortality, inflammation and quality of life. Contrib Nephrol. 2011;168: 39–52.
42. Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. Nephrol Dial Transplant. 2013;28(2):438–46.
43. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–92.
44. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Outcomes associated with serum phosphorus level in males with non-dialysis dependent chronic kidney disease. Clin Nephrol. 2010;73(4): 268–75.
45. Minutolo R, Bellizzi V, Cioffi M, Iodice C, Giannattasio P, Andreucci M, et al. Postdialytic rebound of serum phosphorus: pathogenetic and clinical insights. J Am Soc Nephrol. 2002; 13(4):1046–54.
46. Davenport A, Gardner C, Delaney M. The effect of dialysis modality on phosphate control: haemodialysis compared to haemodiafiltration. The Pan Thames Renal Audit. Nephrol Dial Transplant. 2009;24(10):3209–15.

47. Penne EL, van der Weerd NC, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55(1):77–87.
48. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K. Secondary hyperparathyroidism is associated with higher mortality in men with moderate to severe chronic kidney disease. Kidney Int. 2008;73(11):1296–302.
49. Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, Goodman WG, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012;367(26):2482–94.
50. Rius A, Hernandez-Jaras J, Pons R, Garcia PH, Torregrosa E, Sanchez Canel JJ, et al. Kinetic of calcium, phosphate, magnesium and PTH variations during hemodiafiltration. Nefrología. 2007;27(5):593–8.
51. Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int. 2011;79(12):1370–8.
52. Urena TP, Friedlander G, de Vernejoul MC, Silve C, Prie D. Bone mass does not correlate with the serum fibroblast growth factor 23 in hemodialysis patients. Kidney Int. 2008;73(1): 102–7.
53. Patrier L, Dupuy AM, Granger VA, Chalabi L, Morena M, Canaud B, et al. FGF-23 removal is improved by on-line high-efficiency hemodiafiltration compared to conventional high flux hemodialysis. J Nephrol. 2013;26(2):342–9.
54. Marsell R, Grundberg E, Krajisnik T, Mallmin H, Karlsson M, Mellstrom D, et al. Fibroblast growth factor-23 is associated with parathyroid hormone and renal function in a population-based cohort of elderly men. Eur J Endocrinol. 2008;158(1):125–9.
55. Scialla JJ, Wolf M. Roles of phosphate and fibroblast growth factor 23 in cardiovascular disease. Nat Rev Nephrol. 2014;10(5):268–78.
56. Seiler S, Rogacev KS, Roth HJ, Shafein P, Emrich I, Neuhaus S, et al. Associations of FGF-23 and sKlotho with cardiovascular outcomes among patients with CKD stages 2–4. Clin J Am Soc Nephrol. 2014;9(6):1049–58.
57. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73(4):391–8.
58. Mazairac AH, de Wit GA, Grooteman MP, Penne EL, van der Weerd NC, van den Dorpel MA, et al. A composite score of protein-energy nutritional status predicts mortality in haemodialysis patients no better than its individual components. Nephrol Dial Transplant. 2010;26(6):1962–7.
59. de Roij van Zuijdewijn CL, ter Wee PM, Chapdelaine I, Bots ML, Blankestijn PJ, van den Dorpel MA, et al. A comparison of 8 nutrition-related tests to predict mortality in hemodialysis patients. J Ren Nutr. 2015;25(5):412–9.
60. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Penne EL, Mazairac AH, et al. Clinical predictors of decline in nutritional parameters over time in ESRD. Clin J Am Soc Nephrol. 2014;9(2):318–25.
61. Macdougall IC. Present and future strategies in the treatment of renal anaemia. Nephrol Dial Transplant. 2001;16 Suppl 5:50–5.
62. Locatelli F, Altieri P, Andrulli S, Sau G, Bolasco P, Pedrini LA, et al. Predictors of haemoglobin levels and resistance to erythropoiesis-stimulating agents in patients treated with low-flux haemodialysis, haemofiltration and haemodiafiltration: results of a multicentre randomized and controlled trial. Nephrol Dial Transplant. 2012;27(9):3594–600.
63. van der Weerd NC, den Hoedt CH, Blankestijn PJ, Bots ML, van den Dorpel MA, Levesque R, et al. Resistance to erythropoiesis stimulating agents in patients treated with online hemodiafiltration and ultrapure low-flux hemodialysis: results from a randomized controlled trial (CONTRAST). PLoS One. 2014;9(4):e94434.
64. Szeto CC, Wong TY, Chow KM, Leung CB, Li PK. Oral sodium bicarbonate for the treatment of metabolic acidosis in peritoneal dialysis patients: a randomized placebo-control trial. J Am Soc Nephrol. 2003;14(8):2119–26.

65. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant. 2009;24(4): 1232–7.
66. Morel H, Jaffrin MY, Lux C, Renou M, Fessier C, Petit A, et al. A comparison of bicarbonate kinetics and acid-base status in high flux hemodialysis and on-line post-dilution hemodiafiltration. Int J Artif Organs. 2012;35(4):288–300.
67. Gritters-van den Oever M, Grooteman MP, Bartels PC, Blankestijn PJ, Bots ML, van den Dorpel MA, et al. Post-dilution haemodiafiltration and low-flux haemodialysis have dissimilar effects on platelets: a side study of CONTRAST. Nephrol Dial Transplant. 2009;24(11):3461–8.
68. de Roij van Zuijdewijn C, Nube MJ, Blankestijn PJ, ter Wee PM, van den Dorpel MA, Bots ML, et al. The prescribed dose of low molecular weight heparin increases after assigning patients to hemodiafiltration (HDF) treatment. 2014;11:292A.
69. Schoorl M, Schoorl M, Nube MJ, Bartels PC. Platelet depletion, platelet activation and coagulation during treatment with hemodialysis. Scand J Clin Lab Invest. 2011;71(3):240–7.
70. Borissoff JI, Spronk HM, ten Cate H. The hemostatic system as a modulator of atherosclerosis. N Engl J Med. 2011;364(18):1746–60.
71. Neirynck N, Vanholder R, Schepers E, Eloot S, Pletinck A, Glorieux G. An update on uremic toxins. Int Urol Nephrol. 2013;45(1):139–50.
72. Liabeuf S, Lenglet A, Desjardins L, Neirynck N, Glorieux G, Lemke HD, et al. Plasma beta-2 microglobulin is associated with cardiovascular disease in uremic patients. Kidney Int. 2012;82(12):1297–303.
73. Pletinck A, Glorieux G, Schepers E, Cohen G, Gondouin B, Van LM, et al. Protein-bound uremic toxins stimulate crosstalk between leukocytes and vessel wall. J Am Soc Nephrol. 2013;24(12):1981–94.
74. Meert N, Waterloos MA, Van LM, Dhondt A, Ledebo I, Glorieux G, et al. Prospective evaluation of the change of predialysis protein-bound uremic solute concentration with postdilution online hemodiafiltration. Artif Organs. 2010;34(7):580–5.
75. Chapdelaine I, Mostovaya IM, Blankestijn PJ, Bots ML, van den Dorpel MA, Levesque R, et al. Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration. Blood Purif. 2014;37(3):229–37.
76. Marcelli D, Scholz C, Ponce P, Sousa T, Kopperschmidt P, Grassmann A, et al. High-volume postdilution hemodiafiltration is a feasible option in routine clinical practice. Artif Organs. 2015;39(2):142–9.

Chapter 20
Hemodiafiltration in Children

Michel Fischbach, Ariane Zaloszyc, and Rukshana Shroff

Abstract Hemodiafiltration (HDF) is a safe and highly efficient renal replacement therapy that allows diffusive and convective clearance of uremic toxins across a wide molecular weight range. Advances in technology with the availability of dialysis machines that allow controlled ultrafiltration (UF) and smaller dialysis filters and lines have enabled the use of HDF as a safe technique of routine renal replacement therapy even in small children. In this chapter the technique, advantages and clinical studies on HDF in children are described. We depict our experience in the developing and refining of the HDF technique in children over four decades, and clinical outcomes of intensified daily on-line HDF, particularly on growth. Careful attention to achieving the highest possible convective volume is important as this is likely to improve patient outcome. A clinical trial comparing the outcomes of HDF versus conventional hemodialysis (HD) in children is in progress.

Keywords Hemodiafiltration (HDF) • Hemodialysis (HD) • Convective volume • Diffusion • Ultrapure water • Growth

Introduction

Hemodiafiltration (HDF) was initially described in adults [1] and later used in children in the early 1980s [2]. HDF is the addition of a determined convection volume to HD [3], thereby allowing for blood purification combining diffusive transport of small uremic toxins and convective mass transfer of larger middle-molecular weight uremic toxins. The total convection volume achieved over a HDF session is the sum

M. Fischbach, PhD (✉)
Chef de Service Pédiarie 1, CHU Hautepierre, Av Molière, Strasbourg 67098, France
e-mail: Michel.Fischbach@chru-strasbourg.fr

A. Zaloszyc, PhD
Children Dialysis Unit, University Hospital Strasbourg, Strasbourg, France

R. Shroff, MD, FRCPCH, PhD
Nephrology Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_20

of both the prescribed weight loss and the pre-determined amount of ultrafiltration (UF), with UF replaced by an equal volume of substitution fluid [3]. Recent clinical trials in adults on HDF have suggested that the total convective volume achieved is an independent predictor of survival [4–6]. Advances in technology with the availability of dialysis machines that allow controlled UF and smaller dialysis filters and lines have enabled the use of HDF as a safe technique of routine renal replacement therapy in children [7–9]. In this chapter we describe the technique, advantages and clinical studies on HDF in children.

History of HDF in Children, a Single Centre Experience

HDF in children was first performed in the dialysis unit in Strasbourg, France in July 1981 when the children's dialysis unit separated from the adult unit [10]. Several modifications to the HDF circuit used in adults were required before it could be safely performed in children.

The first aim was to improve volume control: in order to achieve hemodynamic stability over the dialysis session, the osmotic stability of the substitution fluid was a major contributing factor (iso-osmotic hemofiltration substitution fluid). The selection of a suitable dialysis membrane was based on its hydraulic permeability (K_{UF}; coefficient of UF: mL/mm of transmembrane pressure, [TMP]) [11] with an upper limit of the TMP at 300 mmHg. Using the CS Ultrafilter (Polycrylonitrile/ASAHI), post-dilution HDF was performed with a convective flow of one third of the blood flow, and well tolerated with fewer hypotensive episodes compared to conventional HD (Fig. 20.1). In addition, the urea clearance dramatically increased compared to hemofiltration alone, and despite the urea clearance per session increasing fivefold (>5 mL/min/kg body weight), the dialysis tolerance increased with no or rare and mild hemodynamic instability on dialysis [2].

Secondly, the importance of membrane permeability, not only in the range of low molecular weight uremic toxins like urea, but also middle molecular weight uremic toxins and their potential importance was being discovered [10]. Starting in 1981, we monitored dialysis kinetics not only of urea but also of phosphate, inulin, β_2-microglobulin (B2M) and 25-hydroxyvitamin D and noted a significant improvement in the removal of larger molecular weight uremic toxins with HDF compared to HD (Fig. 20.2) [12]. A simultaneous reduction in the need for blood transfusions was noted, even in the era preceding Erythropoietin Stimulating Agent use (Fig. 20.3) [13].

In the early days of starting HDF, the substitution fluid was delivered in bags of sterilized fluid, but no determination of endotoxin levels could be performed. Although this ensured substitution fluid purity, both in terms of its chemical composition and microbiological contamination, its high cost limited the convection volume used per session. Later, on-line HDF technology was developed: dialysis water was filtered through a reverse osmosis system followed by two disposable membranes in the dialysate circuit to produce 'ultra-pure' dialysis fluid (both 'ultra-pure'

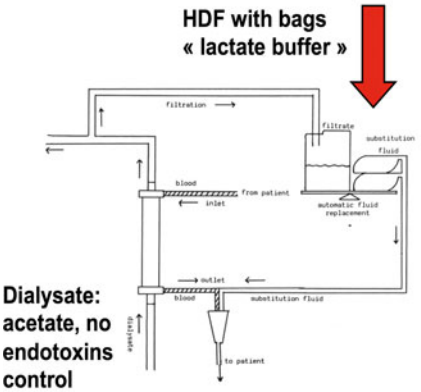


TABLE I - PARAMETERS USED FOR THE STUDY

HD (12 months)	HDF (12 months)
plate (0.92 m2) cuprophane Q_B 120-160 ml/min Q_D 500 ml/min 3 X 5 h/week	capillary (1 m2) PAN Q_B 120-160 ml/min Q_D 500 ml/min 3 X 3 h/week substitution fluid 7-9 (lactate) TMP less than 300 mmHg

TABLE IV - RELATIONSHIP BETWEEN UREA, CREATININE CLEARANCE IN HD (K_{HD}) AND IN HDF (K_{HDF})

	Urea		Creatinine
	ml/min	ml/min/kg body weight	ml/min
K_{HD}	90 ± 2	4.3	93 ± 10
K_{HDF}	131 ± 9	6.3	115 ± 17

TABLE II - RELATIONSHIP IN 6 CHILDREN BETWEEN SERUM LEVELS OF UREA, CREATININE, PHOSPHATE IN HD AND HDF (AT START AND END OF TREATMENT SESSION)

	HD (15 h/week)		HDF (7.5 - 9 h/week)	
	start	end	start	end
urea mmol/l	40±6	16±3	32±4	6±2
creatinine µmol/l	1,080±256	410±167	810±280	240±123
phosphate mmol/l	1.65±0.28	0.9±0.19	1.34±0.15	0.5±0.08

Fig. 20.1 When HDF was first started in our unit, a balance system and bags for the hemofiltration substitution volume were used [2] (Courtesy of Prof. Michel Fischbach)

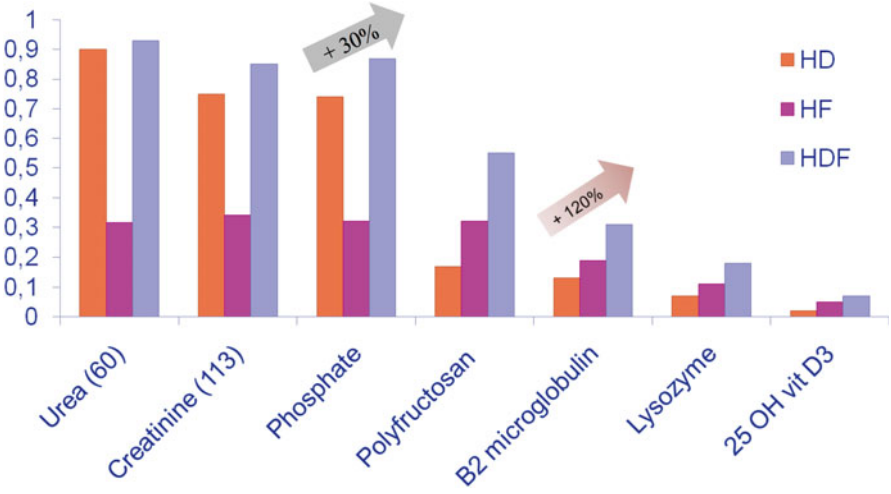
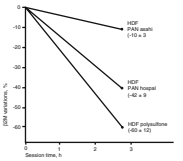


Fig. 20.2 Molecular permeability of the polysulfone membrane: impact of the dialysis modality: *HD* hemodialysis, *HF* hemofiltration, *HDF* hemodiafiltration (Based on data from Ref. [10])

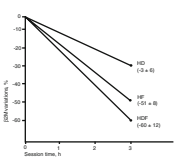
dialysate and sterile substitution fluid) with >100-fold lower bacterial and endotoxin levels than the water used for conventional HD. Thus, on-line HDF technology allowed the use of large volumes of sterile substitution fluid to achieve high convective volumes over a HDF session, without increased cost. This allowed us to perform pre-dilution HDF as well as daily on-line HDF, with substantial

Hemodiafiltration with high permeable membranes in children			
	HD 15 h/ week cuprophane 12 months	HDF 9 h/week PAN 12 months	HDF 9 h/weeks Polysulfone 12 months
TAc urea (mmol/L)	28±4	18±3	20±2
PCRn (g/kg/j)	0.7±0.2	1±0.1	1.8±0.3
Phosphate (mmol/L)	1.65±0.28	1.34±0.15	1.15±0.18
Alumininum prescription (g/day)	3	1.5	0.5
Hemoglobin (g/dl)	7.4	8.3	8.9
Need of transfusion per year	5	2	1
Date	1981	1982	1983

Fig. 20.3 Hemodiafiltration in the era before erythropoietin stimulating agents were available: children on HDF had a significant reduction in the number of transfusion per year to maintain a hematocrit over 20 % (Based on data from Ref. [13])



I. β_2M serum level variations in HDF with different membranes (mean ± SEM, n = 30 sessions).



II. β_2M serum level Variations with a polysulfone membrane versus condition of dialysis management: HF, HD, or HDF (mean ± SEM; n = 30 sessions).

III. HDF treatment in the 5 children described in Part IV

	HDF PAN 150	HDF polysulfone
Treatment	3 x 3 h/week 1.5 years	3 x 3 h/week 3.5 years
β_2M sieving coefficient	0.015 ± 0.001	0.504 ± 0.029
β_2M removal per HDF session, mg	3 ± 0.5	75 ± 4

IV. Evolution of β_2 serum levels in 5 anuric children under HDF treatment

	Jan 83	Jan 84	Jan 85	Jan 86	Jan 87	Jan 88
Mean weight, kg	22 ± 1	23 ± 1.3	24 ± 0.8	25 ± 1.4	26.5 ± 1.5	27.4 ± 1.2
β_2M serum mg/1	35 ± 7.5	42 ± 8	39 ± 4.8	42 ± 6.3	39.6 ± 4.5	41.3 ± 8.2

Fig. 20.4 Despite enhanced removal by hemodiafiltration, serum β2 microglobulin levels remained stable over a 5 year follow-up period in the era when ultrapure dialysate was not yet available and endotoxins levels in the dialysate could not be determined (Reprinted from Fischbach et al. [12]. With permission from S. Karger AG, Medical and Scientific Publishers)

improvements in B2M clearance [12] and improved patient well-being as described below. Our experience with monitoring the dialysis kinetics of middle-molecular weight substances revealed a discrepancy between an improved B2M dialytic removal on HDF, but persistently high blood level of B2M over time (Fig. 20.4)

[12]. We intensified the dialysis dose by using daily pre-dilution HDF with high convection volumes and were able to achieve pre-dialysis B2M blood levels below 20 mg/l, even in anuric children [14]. However, as dialysis efficiency with improved B2M clearance was achieved, the risk of excessive albumin loss through highly permeable membranes was also noted [15]. Applying daily in-centre intensive HDF, we were able to show that children are free of symptoms: there was no post-dialysis recovery time, few or no medication requirements, normal diet and optimized volume control on a free fluid intake [16, 17]. These improvements with daily intensive HDF allowed catch-up growth with normal height in the target mid-parental height range achieved even before kidney transplantation [14, 18].

Requirements for HDF in Children

HDF in children requires dialysis machines that allow careful regulation of UF, highly permeable membranes and sterile fluid for replacement of convective flow. These items are described in detail in the Chaps. 2, 3, 4, 5, 6, 7, 8, 9, and 10 and their adjustment for children is shortly complemented here.

Today, all new dialysis machines allow for both HD and HDF. HDF machines suitable for children are manufactured by Gambro and Fresenius Medical Care (FMC): currently available machines include the Gambro AK200 UltraS and FMC4008 and FMC5008 machines. All these machines are suitable for children above 15 kg body weight. Pediatric lines that are suitable for HDF in children <15 kg would require an extracorporeal volume of less than 80 mL (including both lines and filter), and are available only for the older generation of FMC4008 machines, and currently under manufacture for the FMC5008 machine. Only highly permeable membranes are suitable for HDF, both in adults and children [19].

Writing a HDF Prescription for Children

The dialysis prescription (blood flow, duration of the session and dialysate flow) should be individually adapted to achieve an urea dialysis dose of Kt/V $\geq$1.4, which is a surrogate for predominantly diffusive blood purification [19, 20] as well as the highest possible convective clearance.

The following points should be considered when writing an HDF prescription for children:

1. HDF requires an optimal arterial blood flow of 5–8 ml/min/kg body weight or 150–240 ml/m^2 body surface area [19]. This can be achieved through either a fistula or a central venous line.
2. A high-flux membrane with surface area equal to the child's body surface area is used [19].
3. Dialysate flow of 1.5 times the blood flow is adequate to optimize the diffusive blood purification process using highly permeable membranes for HDF.

4. Convective flow is equal to total UF flow i.e. the sum of the weight loss and the replacement fluid (convective dialysis dose per session).
   - Post-dilution HDF – the convective flow is ≤33 % of the blood flow, and limited by the risk of filter clotting. It typically decreases over the dialysis session (TMP should be limited to less than 300 mmHg).
   - Pre-dilution HDF – the convective flow is set at ≥50 % of blood flow, but optimally can be increased to 75–100 % of blood flow; despite the dilution of the blood potentially impacting negatively on urea clearance, B2M and phosphate dialytic removal is optimized as is the clearance of uremic protein bounded toxins.
5. Optimal anticoagulation is necessary so as to prevent filter clotting, particularly in post-dilution HDF. A single dose of low molecular weight heparin is effective for a 4 h session. Alternatively, a continuous heparin infusion can be used.
6. The dialysate composition is similar to that used in HD, but careful attention to dialysate sodium concentration is important, particularly when high convective volumes are infused, as with pre-dilution HDF. To avoid the risk of a positive sodium balance the dialysate sodium concentration required is lower than in conventional HD.
7. Replacement fluid that is generated on-line from the dialysate must be 'ultrapure' as discussed above. The microbiological purity (bacterial count and endotoxin level) should be determined regularly at one to three monthly intervals.

Advantages of HDF Over Conventional HD: Paediatric Studies

The advantages of HDF over conventional HD can be discussed under the three main mechanisms of the beneficial effects of HDF:

1. *Improved dialysis efficiency and clearance of toxins across a wide molecular weight range*: Middle and large molecular weight compounds such as B2M that normally accumulate in patients with end-stage kidney disease have >70 % better removal on HDF, if compared to low-flux HD [21–23]. Likewise, plasma phosphate has a 30 % greater clearance by HDF [24]. Conflicting data have been published on erythropoietin resistance, which has been linked to reduced inflammation and removal of erythropoiesis-inhibiting factors during treatment with HDF. For further reading on these subjects see Chaps. 11, 12, and 14.
2. *Improved haemodynamic stability*: HDF increases UF and improves intradialytic hemodynamic stability [25], leading to less intradialytic hypotension and faster recovery time post-dialysis, both in children and adults [14, 26]. See also Chap. 17.
3. *Biocompatibility and reduced inflammation*: The use of 'ultrapure' dialysate and increased removal of inflammatory cytokines may reduce inflammation and oxidative stress [14, 18]. See Chap. 13.

Most importantly, these benefits of HDF appear to translate into improved survival. In adults, three randomised controlled trials have suggested improved survival and reduced cardiovascular mortality when higher substitution volumes (>17.4 L and >20 L in the respective studies) were used. In children, HDF leads to impressive catch-up growth with a projected final height approaching target mid-parental height with daily HDF [14, 18].

Using daily HDF, these benefits may be further improved. Our group noted that conventional three-times a week HDF improved B2M dialytic removal but stable high blood levels of B2M persisted (Fig. 20.4). When HDF was given 5 days per week with high convective volumes, predialysis B2M levels decreased below 20 mg/l even in anuric children [14, 16]. Overall, children on intensive daily HDF had symptom free dialysis sessions, no postdialysis recovery time, no or limited medications, an unrestricted diet, optimized blood purification and optimized volume control [14, 16]. The UF required in each dialysis session was minimal, a major prognostic factor for improved patient outcome [3, 14, 17]. Taken together, daily intensive HDF led to an anabolic state and catch up growth, with children achieving a normal height, at or above their target mid-parental height, even before kidney transplantation [14].

Currently, only single centre data are available on the outcomes of HDF in children. An international non-randomised clinical trial is under progress to compare the effects of HDF versus conventional HD on growth and cardiovascular markers in children (HDF, hearts and height [3H] study), with data available in 2017 (ClinicalTrials.gov identifier: NCT02063776).

Conclusions

HDF is a safe and highly efficient renal replacement therapy that allows diffusive and convective clearance of uraemic toxins across a wide molecular weight range. Recent advances in technology have enabled its use as a safe therapy for chronic dialysis even in small children, the most clear benefits being an improved nutritional state and catch-up growth. Careful attention to achieving the highest possible convection volume is important as this is likely to improve patient outcome.

Teaching Points

- Water quality and safety requirements of HDF treatment are similar for children and adults
- In children, the major benefits of HDF over HD are an improvement in nutritional state and catch-up of growth
- In analogy to the concept of high volume HDF in adults, achievement of high (BSA adjusted) convection volumes may be beneficial in children as well

- When high volume HDF is applied, the dialysate sodium concentration should be lower than in HD
- An international non-randomised clinical trial to compare the effects of HDF versus conventional HD in children with respect to growth and surrogate cardiovascular parameters is currently in progress

References

1. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schutterle G. Simultaneous hemofiltration/hemodialysis: an effective alternative to hemofiltration and conventional hemodialysis in the treatment of uremic patients. Clin Nephrol. 1978;9:115–21.
2. Fischbach M, Attal Y, Geisert J. Hemodiafiltration versus hemodialysis in children. Int J Pediatr Nephrol. 1984;5:151–4.
3. Fischbach M, Fothergill H, Zaloszyc A, Seuge L. Hemodiafiltration: the addition of convective flow to hemodialysis. Pediatr Nephrol. 2012;27:351–6.
4. Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
5. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
6. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transpl. 2013;28:192–202.
7. Blankestijn PJ, Ledebo I, Canaud B. Hemodiafiltration: clinical evidence and remaining questions. Kidney Int. 2010;77:581–7.
8. Ledebo I, Blankestijn PJ. Haemodiafiltration-optimal efficiency and safety. NDT Plus. 2010;3:8–16.
9. Maduell F, del Pozo C, Garcia H, et al. Change from conventional haemodiafiltration to on-line haemodiafiltration. Nephrol Dial Transplant. 1999;14:1202–7.
10. Fischbach M, Koehl C, Geisert J. Hemodiafiltration – a superior method of blood purification in children? Contrib Nephrol. 1985;46:162–8.
11. Ficheux A, Ronco C, Brunet P, Argiles A. The ultrafiltration coefficient: this old ‘grand inconnu’ in dialysis. Nephrol Dial Transplant. 2015;30:204–8.
12. Fischbach M, Hamel G, Koehl C, Geisert J. Beta-2-microglobulin in hemodiafiltered children: long-term efficiency follow-up. Nephron. 1989;53:110–4.
13. Fischbach M, Hamel G, Geisert J. Efficiency of high permeable membranes in hemodiafiltration in children: an optimal method of purification. Int J Pediatr Nephrol. 1985;6:251–6.
14. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25:867–73.
15. Potier J, Le RF, Faucon JP, et al. Elevated removal of middle molecules without significant albumin loss with mixed-dilution hemodiafiltration for patients unable to provide sufficient blood flow rates. Blood Purif. 2013;36:78–83.
16. Fischbach M, Fothergill H, Zaloszyc A, Menouer S, Terzic J. Intensified daily dialysis: the best chronic dialysis option for children? Semin Dial. 2011;24:640–4.
17. Movilli E, Gaggia P, Zubani R, et al. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant. 2007;22:3547–52.
18. Schaefer F. Daily online haemodiafiltration: the perfect ‘stimulus package’ to induce growth? Nephrol Dial Transplant. 2010;25:658–60.

19. Fischbach M, Edefonti A, Schroder C, Watson A. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20:1054–66.
20. Goldstein SL. Adequacy of dialysis in children: does small solute clearance really matter? Pediatr Nephrol. 2004;19:1–5.
21. Canaud B, Morena M, Cristol JP, Krieter D. Beta2-microglobulin, a uremic toxin with a double meaning. Kidney Int. 2006;69:1297–9.
22. Cheung AK, Rocco MV, Yan G, et al. Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. J Am Soc Nephrol. 2006;17:546–55.
23. Penne EL, van der Weerd NC, Blankestijn PJ, et al. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. Clin J Am Soc Nephrol. 2010;5:80–6.
24. Penne EL, van der Weerd NC, van den Dorpel MA, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55:77–87.
25. Donauer J, Schweiger C, Rumberger B, Krumme B, Bohler J. Reduction of hypotensive side effects during online-haemodiafiltration and low temperature haemodialysis. Nephrol Dial Transplant. 2003;18:1616–22.
26. Fischbach M, Terzic J, Menouer S, et al. Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol. 2006;21:1746–52.

Chapter 21
Intensified Hemodiafiltration

Francisco Maduell, Raquel Ojeda, and Marta Arias-Guillén

Abstract Mortality in patients under a conventional dialysis regimen of three 4-h sessions per week is four times higher than in the general population older than 65 years and new therapeutic regimens are required to improve patient survival. The thrice-weekly frequency of hemodialysis (HD), established the 1960s, has mainly been accepted and maintained since then for logistic, pragmatic and economic reasons. However, longer and more frequent dialysis sessions have produced excellent survival and clinical advantages. The results of the Tassin experience of long, slow-flow HD were first reported 30 years ago and showed excellent fluid and blood pressure control with the highest survival rates achieved at that time. Since then, multiple publications reported on the superiority of long-duration HD over conventional therapy. On-line postdilution hemodiafiltration (OL-HDF) offers an optimal form of extracorporeal treatment for patients with end-stage kidney disease. This technique, which combines diffusion with a considerable amount of convection, provides the highest clearances per unit of surface area for small, medium and large molecules. In this chapter we describe our experience with OL-HDF in two extended dialysis schemes: short daily OL-HDF and nocturnal, every-other-day, OL-HDF.

Keywords Daily dialysis • Frequent dialysis • Long dialysis • Nocturnal dialysis • Every-other-day dialysis • Occupational rehabilitation • Medication reduction

Introduction

Although the mortality rate for hemodialysis (HD) patients fell by 25 % from 2003 to 2012 in comparison with only 3 % from 1993 to 2002 [1], clinical outcome in this patient groups is still unacceptable poor and has recently been linked to the long inter-dialytic interval [2–4]. The limitations of thrice-weekly conventional HD in

F. Maduell, MD, PhD (✉) • R. Ojeda, MD • M. Arias-Guillén, MD
Department of Nephrology, Hospital Clínic, Villarroel, 170 Barcelona, Catalonia 08036, Spain
e-mail: fmaduell@clinic.ub.es

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_21

preventing the sequelae of chronic kidney disease (CKD), such as cardiovascular disease, CKD-mineral and bone disorder (CKD-MBD), hypertension, metabolic acidosis, hyperkalemia, inflammation, malnutrition and poor quality of life, are well known to the nephrology community [5]. Potential mechanisms for the adverse effects related to intermittent HD have recently been reviewed. [6] Most observational data agree that frequent dialysis schemes reduce fluctuations in metabolic and volume parameters, if compared with thrice-weekly schedules [7]. A recent review suggested that intensified dialysis schemes (daily, nocturnal or every-other-day) significantly improved blood pressure control, CKD-MBD and quality of life [8]. On-line postdilution hemodiafiltration (OL-HDF), which combines diffusion with high convective transport, provides the highest clearances per unit of surface area for small, medium, and large molecules. During the last 10 years, three randomized clinical trials have analyzed OL-HDF survival as a primary end point [9–11]. Only the ESHOL study [10] demonstrated improved survival in patients receiving OL-HDF and recent meta-analyses have confirmed the lower overall and cardiovascular mortality of this modality [12, 13]. This chapter aims to describe our personal experience with OL-HDF in two extended dialysis schemes: short daily OL-HDF and nocturnal, every-other-day, OL-HDF [14–16].

Daily Hemodiafiltration

Introduction

Daily HD has been shown to improve clinical outcomes and laboratory parameters, if compared to intermittent HD. The underlying mechanisms are the more physiological technique, which avoids volume overload and electrolyte and acid-base balance disturbances in the inter-dialytic periods, and better removal of uremic toxins [6]. The combination of daily dialysis and a high convective transport technique, such as OL-HDF, offers both higher removal of middle-sized and large molecules and better tolerance to dialysis, and is currently considered a good treatment option for patients requiring chronic renal replacement therapy [14].

Study Design and Practical Implementation

In 2003, we reported the first experience of combining a more physiological and effective dialysis schedule – daily dialysis – with the dialysis modality that offers the highest solute and uremic toxin removal (OL-HDF) [14]. This single-center, prospective and nonrandomized study, included eight stable patients treated for 4–5 h with 3×/week ‘standard’ OL-HDF (S-OL-HDF), who were switched to 2–2$^{1}/_{2}$h 6×/week ‘daily’ OL-HDF (D-OL-HDF). In both treatment options, bicarbonate based buffer was used, a 1.8 m^2 high-flux polysulfone filter (HF80, Fresenius, Bad Homburg,

Germany), a blood flow (Qb) of 445 ± 54 mL/min (350–560 mL/min), a dialysate flow (Qd) of 800 mL/min minus the infusion flow (Qi 80–150 mL/min) and a Fresenius 4008 monitor. Reinfusion was performed in the postdilution mode. All patients had native arteriovenous fistulas and 15-gauge needles were used in both OL-HDF schedules. Hence, the only changes were the frequency and duration of each session.

Impact of Daily Hemodiafiltration on Various Biomarkers

Although dialysis time was similar in both schedules, an increase in the dialysis dose was obtained with D-OL-HDF, confirming the beneficial effect of the higher frequency. Although weekly spKt/V and weekly eKt/V were similar between the two study periods, the EKR and standard Kt/V, proposed to measure the dialysis dose in dialysis regimens with different frequencies, were 26 % and 48 % higher on D-OL-HDF, respectively. Weekly urea reduction rate (URR) was 52 % higher in the daily schedule. This parameter is especially useful for showing differences between regimens with dissimilar frequencies and can be used for any solute.

Mean reduction ratios for urea, creatinin, osteocalcin, β_2-microglobulin (B2M), myoglobin and prolactin were lower per session with D-OL-HDF, but the weekly reduction ratios were significantly increased on D-OL-HDF (see Fig. 21.1). The increased solute removal was more significant in solutes with greater molecular size or lower intercompartment mass-transfer coefficient (Kc) and could be explained by the creation of solute disequilibrium gradients by resistance to diffusion within tissues

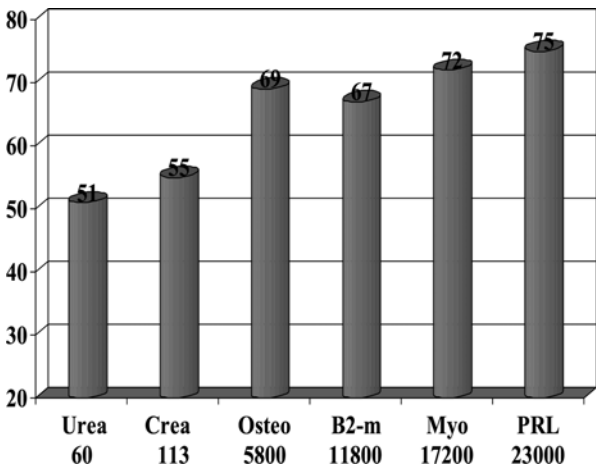


Fig. 21.1 Increase in the weekly percentage removal of a broad spectrum of solutes with short daily on-line hemodiafiltration (D-OL-HDF) in comparison with three times a week on-line hemodiafiltration (OLHDF). Abbreviations are: *Crea* creatinine, *Osteo* osteocalcin, *β2-m* microglobulin, *Myo* myoglobin, *PRL prolactin* (Reprinted from Maduell et al. [14]. With permission from Nature Publishing Group)

and organs. The resistance to diffusion can be quantified as Kc and is molecular size – sensitive. To obtain the same time average concentration in patients treated intermittently, a higher dialysis dose must be used than in daily or continuous treatment. This phenomenon is magnified in solutes with a lower Kc than urea.

Although serum phosphate did not change, phosphate binders (calcium carbonate in seven patients and calcium acetate plus aluminium hydroxide in one patient) were reduced from 7.3 ± 3 tablets/day in S-OL-HDF to 2.9 ± 3 tablets/day after 3 months and 2.85 ± 4 after 6 months ($P < 0.001$) in D-OL-HDF. As reported by Daugirdas et al. [17] and Ayus et al. [18], for better control of predialysis phosphate levels, it is probably not enough to change the frequency of the schedule when the duration of weekly dialysis treatment is not increased as well.

The impact of frequent HD regimens on anemia control remains unclear. Some studies showed minor improvements in hemoglobin (Hb) and reductions in erythropoiesis-stimulating agent (ESA) requirements with more frequent weekly sessions, whereas others did not [8]. In our study, changes in Hb levels or ESA dose were not observed. Ferritin levels decreased over time and iron supplements were raised gradually to improve functional iron deficiency. The use of intravenous iron in daily dialysis experiences has not been clearly specified in the literature, but it is possible that iron needs are higher than in standard HD.

Clinical Impact of Daily Hemodiafiltration

After 6 months of treatment with D-OL-HDF, mean body weight increased by 1.5 kg, which was accompanied by an improvement in appetite and normalized protein catabolic rate (nPCR). These findings were confirmed in a 1-year extension of the study when the gain in body weight reached 3 kg [15]. There were no changes in nutritional parameters in the control group. A similar experience was published in children who were treated with daily predilution OL-HDF [19]. The authors demonstrated improved catch-up growth and significant weight gain with D-OL-HDF, which was related to better nutritional status and less uremic protein wasting, and possibly with a better response to growth hormone administration.

The most common cause of mortality in chronic HD patients is cardiovascular disease, amounting up to 50 % of cases. In our experience, the switch to D-OL-HDF improved several risk factors, such as hypertension, hyperuricemia and hyperhomocysteinemia. Although our patients were relatively well controlled at baseline (only three patients were hypertensive and two were receiving drugs), better blood pressure control was achieved without antihypertensive medications. In addition, we observed a marked regression of left ventricular hypertrophy (LVH) and left ventricular mass index (LVMI) 6 months after switching from S-OL-HDF to D-OL-HDF.

In all patients who were treated with D-OL-HDF, the treatment schedule was well accepted and tolerated. There were no local infections, thrombosis or bleeding of the vascular access. No changes were observed in the frequency of nausea, dizziness, cramps, or hypotensive episodes. In the first 4 weeks, a rapid improvement was reported in headache (n = 3), sleep (n = 3), sexual disorders (n = 2), thoracic pain

(n = 1), appetite (n = 5) and thirst (n = 2). The most apparent benefit was the reduction in the mean post-dialysis fatigue intensity score, from 1.88 ± 1.2 in S-OL-HDF to 0.38 ± 0.7 in D-OL-HDF (P < 0.01), and the mean fatigue duration score from 1.75 ± 1.4 in S-OL-HDF to 0.25 ± 0.5 in D-OL-HDF (P < 0.01).

Summary of Daily Hemodiafiltration

D-OL-HDF is a well tolerated dialysis scheme, which improves clinical outcome and quality of life. For logistic and economic reasons, however, this modality should be restricted to certain patient groups, such as those with severe cardiovascular disease not allowing long inter-dialytic periods and patients with poorly controlled hypertension, as recommended by the European Best Practice Clinical Guidelines [20]. D-OL-HDF schedule is also suitable for patients with hyperphosphatemia, but only if accompanied by an increased duration of the dialysis treatment. See Table 21.1.

Table 21.1 Practical recommendations for intensified HDF schemes

	Short daily OL-HDF	Nocturnal, every-other-day OL-HDF
Td (min)	150–180	420–480
Qb (mL/min)	400–500	400–500
Qd (mL/min)	500–800	300–400
Membrane surface (m^2)	1.4–2.0	1.1–1.4
UF coefficient (ml/mmHg/h)	>40	>40
Qi (mL/min)	100–120	100–120
Replacement vol. (L/ses)	14–18	45–55
Replacement vol. (L/week)	84–108	157–192
P dialysate supplementation	No	Yes

Teaching Points (I)
Daily hemodiafiltration recommended in

- Severe cardiovascular disease
- Poorly controlled hypertension
- Hyperphosphatemia

Clinical advantages of daily hemodiafiltration

- Higher dialysis dose (Kt/V)
- Improved nutritional state
- Regression of LVH
- Improved phosphate control
- Reduction in phosphate binders and antihypertensive medication

Nocturnal, Every-Other-Day Hemodiafiltration

Introduction

More than 30 years have passed since the Tassin group reported their experience of long, slow-flow HD sessions, showing excellent blood pressure and fluid control with the highest survival rates achieved at that time [21]. Since then, multiple publications have demonstrated the superiority of long-duration HD (8 h) over conventional therapy (3–4 h) in terms of blood pressure control, reduction of LVH and reduced serum phosphate levels, often allowing phosphate binders to be discontinued [22–24]. Apart from these clinical advantages, longer (nocturnal) HD also improves quality of life and patient survival [25]. Interest in this thrice weekly prolonged HD modality has increased in the last 10 years, resulting in publications from Canada [23], Germany [24], USA [25], the United Kingdom [26], and Turkey [27]. An every-other-day HD scheme has been used by the Lecce group in Italy since 1972. Survival at 10 years was 60 %, with a lower incidence of ischemic heart disease, stable high depurative efficiency and improvements in anemia, acid-base and nutritional status [28].

Study Design and Practical Implementation

Our experience of combining a more physiological and effective dialysis schedule – long (nocturnal) and more frequent (every-other-day) dialysis – with the dialysis modality that offers the highest solute and uremic toxin removal (OL-HDF) was the first reported in the literature. The study began in September 2007, and the first data published were the results of 26 patients receiving this dialysis schedule for at least 12 months. The study was initially designed as a cross-sectional study, which compared the effect of a switch from 4–5 h 3×/week OL-HDF to 7–8 h nocturnal, every-other-day OL-HDF with the same (20–30 L) or higher (35–50 L) convective volume to evaluate the impact of this schedule on solute removal and analytical and clinical outcomes [16]. Since the publication of these data, we have increased the number of patients to 52, and 26 patients have completed 24 months of follow up (unpublished data). As all these patients were stable and had good prospects for improved occupational, psychological and social rehabilitation, they were younger than the general dialysis population. In nocturnal dialysis schemes, patients are free to carry out their routine activities during the day, which enhances their quality of life.

At baseline, OL-HDF parameters consisted of conventional OL-HDF, 4–5 h 3×/week with bicarbonate buffered dialysate, 1.4–1.8 m^2 high-flux helixone filters (FX60 or FX80, Fresenius), Qb of 440 ± 33 mL/min (400–500 mL/min), Qd 800 mL/min, Qi 90–110 mL/min and a Fresenius 4008 or 5008 dialysis monitor. Reinfusion was always performed in the postdilution mode. All patients had native arteriovenous fistulae and only 15-G needles were used. The duration of the sessions increased from 273 ± 19 min (240–300 min) at baseline to 471 ± 22 min

(420–480 min) in nocturnal every-other-day OL-HDF. Qb was 439 ± 33 mL/min at baseline and 421 ± 32 mL/min at 12 months. The convection volume was 26.7 ± 2 L at baseline, 27.5 ± 2 with the unchanged volume and 42.9 ± 4 L with the higher volume. Once these patients finished the 12-month follow-up, all received the maximum convective volume, the average being 45.8 ± 4 L. This study was performed with a new generation of dialysis machines with auto-substitution systems as described in Chaps. 5, 6, 7, 8, 9, and 10. We have used these 5008 monitors since 2013 and observed a 13 % increase in the convective volume [29].

During the study, the surface area of the dialyzers was reduced to 1.0–1.4 m^2, while Qd fall to 500 mL/min. At present, it is unknown whether a high Qd improves convective transport. Recently, we reported our experience of varying the Qd (300, 400, 500, 600 and 700 ml/min) on convection volume and removal efficacy in 59 patients treated with OL-HDF. As expected, dialysate volume increased from 86.5 ± 4 L (Qd 300 ml/min) to 201 ± 10 L (Qd 700 ml/min) per session, while changes in the amount of substitution volume were not observed. Kt increased from 67.98 ± 6.9 L (Qd 300 ml/min) to 75.53 ± 7.3 L (Qd 700 ml/min). No changes were observed in other medium and large molecules studied. As the variation of Qd in OL-HDF did not change the convection volume we recommend reducing it as far as possible to ensure an adequate dialysis dose at the lowest consumption of water and dialysis concentrate [30].

Impact of Nocturnal Every-Other- Day Hemodiafiltration on Various Biomarkers

To match the dialysis dose in frequent dialysis regimens, stdKt/V has been proposed, and in comparison with thrice-weekly dialysis schemes, our study employed a higher dose per session. Lecce [28] reported a weekly Kt/V of 4.6, which is comparable to a stdKt/V of 2.36, while in our study stdKt/V increased from 1.75 at baseline to 3.77 at the end of the study [16].

All studies of long-duration dialysis have reported excellent anemia control. Initially, we observed a reduction in ESA dosing, while at the end of the study, ESA was discontinued in 29 % of the patients [16]. In a subsequent follow-up in a larger number of patients, ESA dosing fall by 40 % and was discontinued in 35 % of the patients, while the erythropoietin resistance index (ERI) decreased by 50 %.

During follow-up, bicarbonate levels increased significantly. Comparable results are reported by Ok et al. [27] with nocturnal dialysis and by the Lecce experience with every-other-day dialysis [28]. As expected, blood-urea-nitrogen (BUN) and serum creatinin levels were also significantly reduced.

We also found better phosphate control (pre-treatment phosphate decreased from 4.93 to 3.74 mg/dL) and a decreased need for phosphate binders, from 77 to 4 %. Actually, addition of phosphorus supplements in the dialysate was required in 55 % of the patients (see Fig. 21.2). This improved phosphate control could be explained by the sum of several factors. First, the dialysis dose was higher than in other studies; second, some studies have demonstrated that OL-HDF increases phosphate

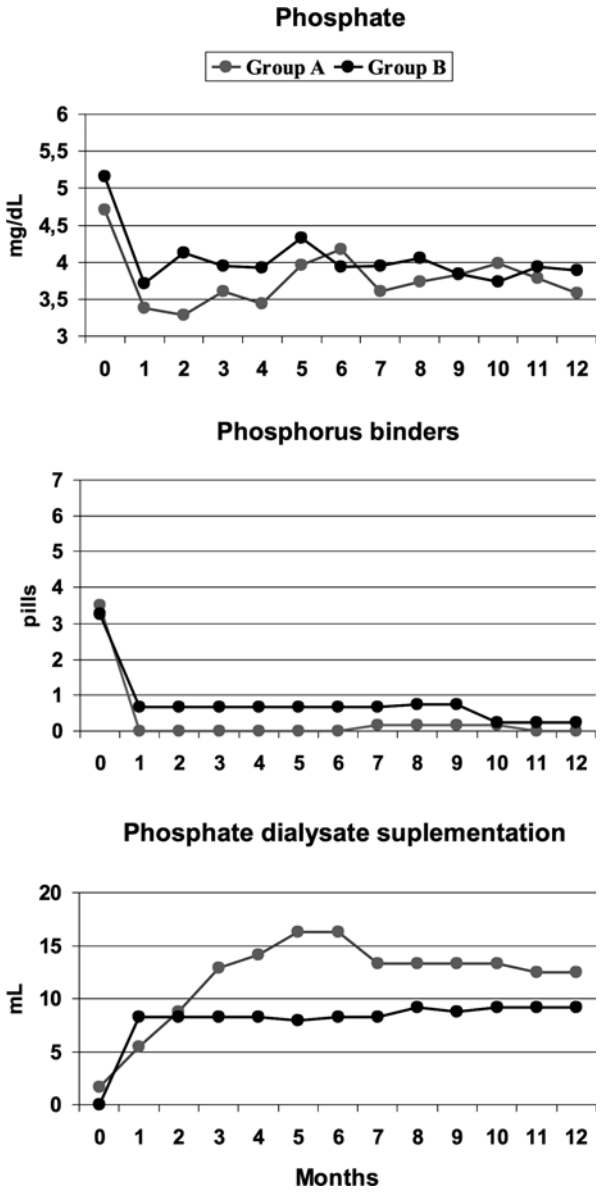


Fig. 21.2 Evolution of serum phosphate, phosphorus binders and phosphate dialysis supplement when switching from thrice-weekly OL-HDF to nocturnal every-other-day OL-HDF. Patients were randomized to 6 months with the same convective volume as previously (20–30 L) followed by 6 months with a higher (35–50 L) convective volume (*Group A*) or to the same two schedules but in reverse order (*Group B*) (Reprinted from Maduell et al. [16]. With permission from Oxford University Press)

depuration with a reduction in predialysis levels [31, 32]. Finally, the increased frequency (every-other-day) is another advantage, as studies of daily nocturnal dialysis have observed excellent phosphate control without phosphate binders and with

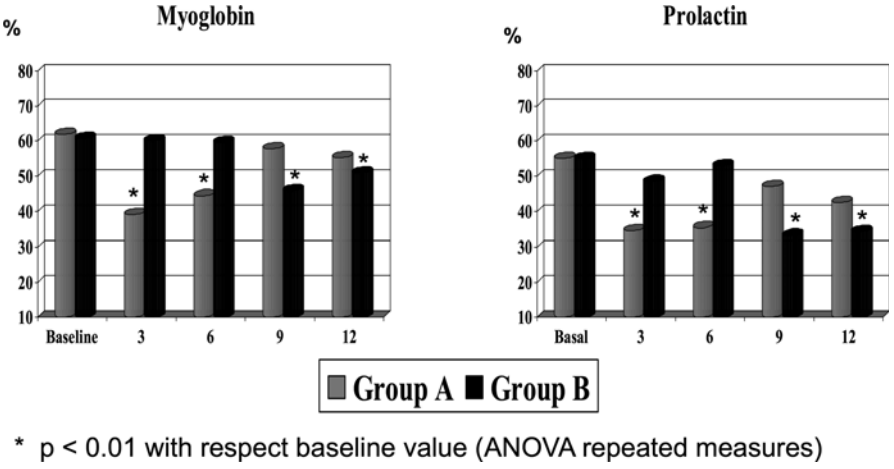


Fig. 21.3 Comparison of percentages of the reduction ratio in myoglobin (17,184 Da) and prolactin (23,000 Da) for each study situation. Group A (n = 12): convective volume of 20–30 L for the first 6 months followed by 6 months of 35–50 L. Group B (n = 12): convective volume of 35–50 L for the first 6 months followed by 6 months of 20–30 L (Reprinted from Maduell et al. [16]. With permission from Oxford University Press)

phosphate supplementation in the dialysate [33, 34]. In children, Thumfart et al. also reported a significant reduction in serum phosphate and PTH levels in both dialysis modalities (NHD and NHDF) in comparison with standard HD, despite discontinuation of phosphate binders [5].

Surprisingly, plasma β2M levels did not decrease during follow-up, despite a significant increase in convection volume, treatment time and frequency. Of note, Ok et al. [27] did not observe reduced pre-dialysis β2M levels just by changing the dialysis duration. The result of β2M removal, as a marker of middle molecule solutes, largely depends on convection processes. In our study, there were no differences between values at baseline and at 6 months with the same convective volume, indicating that removal of β2M mainly depends on the total convective volume, independent of the dialysis time.

Different patterns of solute removal were observed, which were related to dialysis time, convection volume, and/or Qi. To confirm this clinical observation, we performed a new study to evaluate the influence of dialysis duration and infusion flow on the removal of different molecular weight solutes and to verify the usefulness of two-compartment mathematical models in quantifying the changes in removal kinetics when the type of dialysis is changed. In this study, the removal of β2M was significantly increased after changes in both Qi and treatment duration, resulting in an 11 % higher reduction ratio, on average, by doubling the treatment time, and a 6 % improved reduction ratio by doubling convection. These results were confirmed in the mathematical two-compartment model [35]. The removal of larger molecules, such as myoglobin and prolactin, was significantly lower when the same convection volume was applied (see Fig. 21.3). For these high molecular weight molecules the impact of Qi is clearly independent of dialysis time [35].

Clinical Impact of Nocturnal Every-Other-Day Hemodiafiltration

Mean body weight (measured as dry weight after dialysis) increased from 70.1 ± 19 to 72.2 ± 19 Kg ($P < 0.01$) and was accompanied by a greater interdialytic weight gain and protein intake. The improvement in nutrition was not accompanied by changes in inflammation markers, probably because the patients were not previously inflamed and received treatment with biocompatible dialyzers, ultrapure dialysis fluid and convective techniques. These nutritional advantages could also be explained by the reduced fluid overload and uremic milieu after the switch to 7–8 h nocturnal, every-other-day OL-HDF. These results have been corroborated by Thumfart et al. in children [5].

Regarding cardiovascular risk factors, Chan et al. found that the switch from conventional HD, three 4 h sessions per week, to nocturnal HD, 8–10 h six nights per week, resulted in an improvement in the heart rate response to pulsatile blood pressure changes (baroreceptor response and arterial compliance) [36]. In our study, blood pressure control improved and only 8 % of patients required antihypertensive medications at the end of the observation period. In the study by Thumfart et al. the switch from conventional HD to NHD and NHDF resulted not only in discontinuation of antihypertensive therapy in five out of seven children but also in fewer intradialytic hypotensive episodes [5]. Another independent cardiovascular risk factor strongly associated with mortality in dialysis patients is LVH, which is present in 70–80 % of this population. Echocardiographic assessment revealed a 12 % decrease in LVMi after 1 year.

In our experience of 52 patients, 60 % were working and continued working throughout the study with practically no absenteeism, in many different occupations, varying from restaurant workers to a university professor. All patients completed a fatigue index questionnaire on the intensity, duration and frequency of postdialysis fatigue [37], which showed no significant changes over time.

Summary of Nocturnal Every-Other-Day Hemodiafiltration

Conversion from 4–5 h thrice weekly OL-HDF to 7–8 h every-other-day OL-HDF shows excellent clinical tolerance and patient acceptance, adequate social and occupational rehabilitation, better dialysis adequacy, marked improvement in nutritional status, regression of LVH, good phosphate and hypertension control, and a marked reduction of phosphate binders and antihypertensive medication. Different patterns of solute removal were observed, which were related to dialysis time, convective volume and/or to the infusion flow rate. Therefore, long-term, nocturnal, in-center, every-other-day OL-HDF with high convective volumes appears to be a good therapeutic dialysis scheme with improvements in clinical and social-occupational rehabilitation.

Intensified Hemodiafiltration Schemes: Conclusion

D-OL-HDF is a well tolerated dialysis scheme with adequate clinical outcomes and improved quality of life. Due to logistic and economic reasons, however, this modality should be restricted to patients with severe cardiovascular disease and/or poorly controlled hypertension. In case of hyperphosphatemia D-OL-HDF needs to be accompanied by an increase in dialysis time. Nocturnal every-other-day OL-HDF shows excellent clinical tolerance and patient acceptance, adequate social and occupational rehabilitation, better dialysis adequacy, marked improvement in nutritional status, regression of LVH, good phosphate and hypertension control and a marked reduction of phosphate binders and antihypertensive medication. This modality could be prescribed to patients who need to improve clinical and biochemical parameters (hypertension, hyperphosphatemia and other cardiovascular risk factors) and social-occupational rehabilitation. Our recommendations for intensified HDF schemes are summarized in Table 21.1.

Teaching Points (II)
Nocturnal every-other-day hemodiafiltration recommended for/in

- Optimal work-life balance
- Poorly controlled hypertension
- Hyperphosphatemia

Clinical advantages of Nocturnal every-other-day hemodiafiltration

- Higher dialysis dose (Kt/V)
- Improved nutritional state
- Regression of LVH
- Improved phosphate control
- Reduction in phosphate binders and antihypertensive medication

References

1. United States Renal Data System. 2014 annual data report: epidemiology of kidney disease in the United States. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.
2. Flythe JE, Lacson Jr E. Outcomes after the long interdialytic break: implications for the dialytic prescription. Semin Dial. 2012;25:1–8.
3. Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med. 2011;365:1099–107.
4. Krishnasamy R, Badve SV, Hawley CM, et al. Daily variation in death in patients treated by long-term dialysis: comparison of in-center hemodialysis to peritoneal and home hemodialysis. Am J Kidney Dis. 2013;61:96–103.
5. Thumfart J, Puttkamer CV, Wagner S, Querfeld U, Muller D. Hemodiafiltration in a pediatric nocturnal dialysis program. Pediatr Nephrol. 2014;29:1411–6.

6. Georgianos PI, Sarafidis PA. Pro: should we move to more frequent haemodialysis schedules? Nephrol Dial Transplant. 2015;30:18–22.
7. Zhang H, Schaubel DE, Kalbfleisch JD, et al. Dialysis outcomes and analysis of practice patterns suggests the dialysis schedule affects day-of-week mortality. Kidney Int. 2012;81:1108–15.
8. Diaz-Buxo JA, White SA, Himmele R. Frequent hemodialysis: a critical review. Semin Dial. 2013;26:578–89.
9. Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
10. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
11. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28:192–202.
12. Mostovaya IM, Blankestijn PJ, Bots ML, et al. Clinical evidence on hemodiafiltration: a systematic review and a meta-analysis. Semin Dial. 2014;27:119–27.
13. Nistor I, Palmer SC, Craig JC, et al. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. Am J Kidney Dis. 2014;63:954–67.
14. Maduell F, Navarro V, Torregrosa E, et al. Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. Kidney Int. 2003;64:305–13.
15. Maduell F, Navarro V, Rius A, et al. Improvement of nutritional status in patients with short daily on-line hemodiafiltration. Nefrologia. 2004;24:60–6.
16. Maduell F, Arias M, Duran CE, et al. Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative. Nephrol Dial Transplant. 2012;27:1619–31.
17. Daugirdas JT, Chertow GM, Larive B, et al. Effects of frequent hemodialysis on measures of CKD mineral and bone disorder. J Am Soc Nephrol. 2012;23:727–38.
18. Ayus JC, Achinger SG, Mizani MR, et al. Phosphorus balance and mineral metabolism with 3 h daily hemodialysis. Kidney Int. 2007;71:336–42.
19. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25:867–73.
20. Tattersall J, Martin-Malo A, Pedrini L, et al. EBPG guideline on dialysis strategies. Nephrol Dial Transplant. 2007;22 Suppl 2:ii5–21.
21. Charra B, Calemard E, Cuche M, Laurent G. Control of hypertension and prolonged survival on maintenance hemodialysis. Nephron. 1983;33:96–9.
22. Bayliss G, Danziger J. Nocturnal versus conventional haemodialysis: some current issues. Nephrol Dial Transplant. 2009;24:3612–7.
23. Bugeja A, Dacouris N, Thomas A, et al. In-center nocturnal hemodialysis: another option in the management of chronic kidney disease. Clin J Am Soc Nephrol. 2009;4:778–83.
24. David S, Kumpers P, Eisenbach GM, Haller H, Kielstein JT. Prospective evaluation of an in-centre conversion from conventional haemodialysis to an intensified nocturnal strategy. Nephrol Dial Transplant. 2009;24:2232–40.
25. Lacson Jr E, Xu J, Suri RS, et al. Survival with three-times weekly in-center nocturnal versus conventional hemodialysis. J Am Soc Nephrol. 2012;23:687–95.
26. Powell JR, Oluwaseun O, Woo YM, et al. Ten years experience of in-center thrice weekly long overnight hemodialysis. Clin J Am Soc Nephrol. 2009;4:1097–101.
27. Ok E, Duman S, Asci G, et al. Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis: a prospective, case-controlled study. Nephrol Dial Transplant. 2011;26:1287–96.
28. Mastrangelo F, Alfonso L, Napoli M, DeBlasi V, Russo F, Patruno P. Dialysis with increased frequency of sessions (Lecce dialysis). Nephrol Dial Transplant. 1998;13 Suppl 6:139–47.
29. Maduell F, Rodriguez N, Sahdala L, et al. Impact of the 5008 monitor software update on total convective volume. Nefrologia. 2014;34:599–604.

30. Maduell F, Ojeda R, Arias M, et al. Optimizing dialysate flow in online hemodiafiltration. Nefrologia. 2015. doi: 10.1016/j.nefro.2015.06.019 [in press].
31. Davenport A, Gardner C, Delaney M. The effect of dialysis modality on phosphate control: haemodialysis compared to haemodiafiltration. The Pan Thames Renal Audit. Nephrol Dial Transpl. 2012;25:897–901.
32. Penne EL, van der Weerd NC, van den Dorpel MA, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55:77–87.
33. Lockridge Jr RS, Anderson H, Coffey L, et al. Nightly home hemodialysis in Lynchburg, Virginia: economic and logistic considerations. Semin Dial. 1999;12:440–7.
34. Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A. Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. Kidney Int. 1998;53:1399–404.
35. Maduell F, Sanchez J, Net M, et al. Mathematical modeling of different molecule removal on on-line haemodiafiltration: influence of dialysis duration and infusion flow. Blood Purif. 2015; 39:288–96.
36. Chan CT, Shen XS, Picton P, Floras J. Nocturnal home hemodialysis improves baroreflex effectiveness index of end-stage renal disease patients. J Hypertens. 2008;26:1795–800.
37. Sklar A, Newman N, Scott R, Semenyuk L, Schultz J, Fiacco V. Identification of factors responsible for postdialysis fatigue. Am J Kidney Dis. 1999;34:464–70.

Chapter 22
Are There Any Disadvantages of Hemodiafiltration?

Peter J. Blankestijn and Jeroen P. Kooman

Abstract Online postdilution hemodiafiltration (HDF) has been related to an improved patient survival as compared to HD, especially when high convection volumes are applied. Apart from this favorable result, however, online-HDF may evoke side effects that may counteract part of its benefits. Moreover, specific draw backs, related to the set up and maintenance phases of HDF treatment, may hinder the implementation of online HDF on a large scale. So, what are the disadvantages when performing HDF in every day clinical practice? From a medical perspective these may include safety concerns related to the large amounts of substitution fluids directly infused into the patients, the unintended removal of nutrients and other useful compounds including medication, and activation of blood cells. From a financial perspective additional costs may be of relevance. From a practical perspective the main downside of HDF is that starting up a HDF program needs extra efforts of the dialysis staff. In this chapter we discuss the above mentioned issues.

Keywords Hemodiafiltration • Safety • Side effects • Disadvantages

Introduction

After the publication of three recent large randomized controlled trials (RCT) comparing online HDF with HD [1–3], and four meta-analyses on convective therapies [4–7], it seems appropriate to address the question whether there are any side effects, disadvantages or downsides of online hemofiltration (HF) or -HDF. To the best of our knowledge, there are no studies specifically designed to address that question.

P.J. Blankestijn, MD (✉)
Department of Nephrology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands
e-mail: p.j.blankestijn@umcutrecht.nl

J.P. Kooman, MD, PhD
Division of Nephrology, Department of Internal Medicine, University Hospital Maastricht, PO Box 5800, Maastricht, Limburg 6202AZ, The Netherlands
e-mail: Jeroen.kooman@mumc.nl

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_22

We will discuss the subject from a medical, practical and financial/economic perspective, with a primary focus on online HDF, which is currently the most frequently performed convective technique.

Medical Perspective

Possible disadvantages which are discussed in this chapter are related to the sterility of the infusion fluid and the subsequent possibility of inflammatory reactions, the loss of nutritional and other relevant substances, and endothelial or blood cell activation during the treatment.

Sterility of Infusion Fluid

Theoretically, infusion of substitution fluid, when unsterile, might provoke inflammatory and febrile reactions. In clinical practice, however, there is no evidence that even when performed on a wide scale, online HDF contributes to inflammatory or pyrogenic reactions when performed according to the recommendations of manufacturers and guidelines. From a study on 11.258 online HDF sessions in 97 CONTRAST patients over a 1 year period it appeared that the ultrapure dialysis fluid was compliant with bacteriological (bacterial count <0.1 CFU/ml) and endotoxin (LAL <0.03 EU/ml) reference levels in 99.3 % and 98.7 % of the samples, respectively. Elevated bacterial and endotoxin levels were not confirmed in repeated samples, suggesting sampling-induced contamination [8].

These results confirmed those of earlier studies. Canaud et al. reported that no intra-dialytic interleukin-1 receptor antagonist (IL1-RA) induction was detected during a 3 month observational period in 16 patients treated with online HDF [9]. In a study by Pizzarelli et al., no pyrogenic reactions were observed during 4,284 online HDF treatments in 13 patients over a period of 6 years [10]. Comparing the effects of online HDF with low flux HD on systemic inflammation, in a cross-over study in 27 patients who were switched from low flux HD to onine HDF and vice versa, differences in inflammatory parameters such as IL-1 RA, TNF-alpha, and C-reactive protein (CRP) were not observed between the two techniques [11]. Moreover, in a sub-study of CONTRAST in 405 patients, both CRP and interleukin 6 (IL6) showed a significant difference over time in favor of online HDF as compared to HD during 3 years of follow up [12].

Summarizing the available evidence, there is no indication that online HDF, when performed according to accepted quality standards, results in an increased incidence of pyrogenic reactions. The data also show that indeed adequate quality water can be produced over a prolonged period of time and that online HDF does not aggravate the micro-inflammatory state that is commonly observed in ESKD patients. Rather the contrary.

Nutritional Factors: Loss of Amino Acids, Albumin, Trace Elements and Albumin

Due to the larger pore size of the membranes and the high convection volumes, online filtration techniques might lead to unwanted losses of essential nutritional substances, such as amino acids, albumin, trace elements and water soluble vitamins.

With regard to the loss of amino acids, plasma levels of total, essential and branched-chain amino acids decreased by respectively 24 %, 23 % and 18 % during a single session of acetate free biofiltration (AFB) with a filtration volume of approximately 12 L [13].

Albumin loss has been quantified in various studies. Combarnous et al. showed a mean albumin loss of 4 g per treatment during predilution online HDF in a single-treatment study in seven patients using polysulfone membranes [14]. The major part of albumin loss occurred by convective removal, while only a small part (0.7 mg) was removed by adsorption. Subsequent studies showed lesser degrees of albumin loss during online HDF. When comparing super-flux HD (using albumin permeable membranes) with both pre- and postdilution online HDF, albumin loss was highest during superflux HD (>2 g/treatment), followed by postdilution (around 1 g/treatment) and predilution onine HDF (around 0.5 g/treatment) [15]. Using two different types of high flux polysulfone membranes, Krieter et al. observed a mean albumin loss of respectively 1430 mg/session and 809 mg/session in a study on eight patients during postdilution online HDF with filtration volumes well above 20 L per session [16], as shown in Fig. 22.1. A substantial higher mean albumin loss was observed in the study of Fournier et al. (3,134 mg/session), although also a significant variation (SD 2,450 mg) was observed) [17]. From this study it appeared that the dialyzer, as

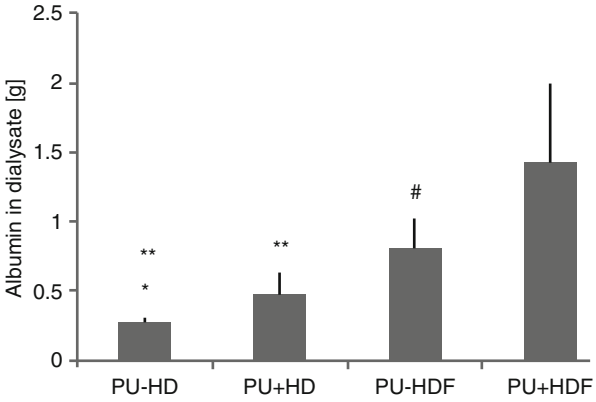


Fig. 22.1 Albumin loss in dialysate of a single session of HD and online post-dilution HDF with two high-flux membranes (PU− and more permeable PU+). Mean and standard deviations. *P<0.05 vs PU+ HD; **P<0.001 versus PU− HDF and PU+ HDF; #P=0.0002 versus PU+ HDF (Reprinted from Krieter et al. [16]. With permission from Oxford University Press)

well as transmembrane pressure (TMP), infusate flow, and the use of automatic pressure adjustment by the module were important determinants of albumin loss [10]. That albumin loss during online HDF treatment is dependent both on the filtration volume and the type of membrane was recently confirmed in a controlled study, which however only assessed albumin loss during the first hour of treatment [18]. The clinical relevance of some extra albumin loss during post dilution online HDF, however, is uncertain. Fournier et al. did not observe a relation between albumin loss and nutritional parameters. Moreover, RCTs comparing HD with online HF or -HDF, did not show a negative effect of these modalities on nutritional parameters or serum albumin [19, 20]. In CONTRAST, the decline in serum albumin levels over a 3 year period was comparable between online HDF and low flux HD [12]. Likewise, differences in serum albumin levels were not observed between low flux HD and online HF during a 12 month follow up period in a randomized study in 40 patients. In the latter study, insulin-like growth factor-1 (IGF-1), as a parameter of nutritional status, remained stable during online HF but declined in the HD group [19].

Cross et al. did not observe a difference in trace elements such as zinc and selenium levels between 44 patients who switched to online HDF and 34 patients who remained on high flux HD [21]. In the same study, online HDF did also not affect serum levels of vitamin B12 and folate. However, the majority of patients in this study used folate supplementation, whereas it has been shown that folate can be removed by both high flux HD and online HDF [14]. The same holds true for vitamin C, which can result in a deficiency of this vitamin when replenished by oral supplementation [22]. Still, differences in the reduction ratios of vitamin C (51 % versus 53 %) were not observed when comparing 15 patients who were treated with high flux HD with 14 patients treated with online HDF [22]. In a study in 19 patients using paired filtration dialysis (a modified HDF technique) with an infusion rate of 45–60 ml/min, mean plasma vitamin C levels decreased from 1.87 to 0.98 μg/ml. The mean loss of vitamin C was 66 mg session. It was estimated that approximately two-thirds of the loss occurred by diffusion and one-third by convection. In this study, no comparison was made with HD [23], see Fig. 22.2.

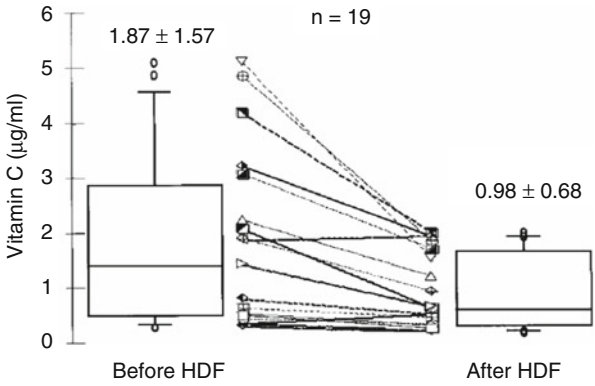


Fig. 22.2 Loss of vitamin C during treatment with HDF in 19 patients. Samples were collected before and after HDF, and total vitamin C levels were determined using an HPLC fluorescence method (Reprinted from Morena et al. [23]. With permission from Oxford University Press)

Concluding, loss of amino acids and albumin may occur during treatment with online HDF. The magnitude of albumin loss is related to the type of the membrane used, the amount of convection volume achieved and the magnitude of TMP applied. At present, no solid evidence exists that these losses have important clinical consequences for the patient, but it should be mentioned that only limited data are available on this subject. There is also no clear evidence for a clinically relevant difference in the loss of trace elements, or water soluble vitamins between on-line convective techniques and standard HD. Nevertheless, as in HD, water soluble vitamins should be substituted in patients treated with on-line filtration techniques.

Antioxidant Status

The decline in vitamin C levels and/or loss of other antioxidant substances might affect the anti-oxidant status of the patient [23]. In a RCT comparing predilution online HF with low flux HD, after 1 year of treatment, Beerenhout et al. observed a decline in antioxidant status without differences between groups. In this study, the relation between changes in vitamin C levels and antioxidant status, however, was not assessed [19]. In another study, comparing 25 patients who were treated with HDF with on-line regeneration of infusate with 15 patients who were treated with high flux HD, no significant difference in antioxidant status was observed [24]. In contrast to these results, after 9 months an increase in antioxidant status was observed in an uncontrolled study in nine patients who switched from standard HD to online HDF [25].

Summarizing, whereas on line filtration techniques may influence antioxidant status, currently there is no firm evidence for a major difference between these techniques and HD.

Activation of Blood Cells

During HD, both activation of endothelial cells and circulating blood cell elements has been described. Notably, the degree of activation appeared to depend on patient characteristics rather than on the type of dialyzer used [26]. However, as both hemoconcentration and TMP within the dialyzer are greatly increased in online HDF, it has been suggested that these unwanted side effects of dialysis treatment are more pronounced in online HDF as compared to HD. In this respect it is interesting to note, that the serum levels of the endothelial surface marker ICAM-1 were significantly higher after postdilution online HDF than after predilution online HDF. Interestingly, phagocytic function of neutrophils increased after predilution online HDF but decreased after postdilution OL-HDF, while the lymphocytic proliferative response was higher after predilution online HDF. In a crossover study in five patients, Sakurai observed less monocyte activation as a result of lower IL-6 levels during predilution online HDF (substitution volume 50 L/session) versus no

change in post-dilution online HDF (10 L/session) [27]. A sub-analysis in 19 CONTRAST patients showed a more pronounced drop in the number of circulating platelets and a higher expression of the platelet surface marker P-selectin (CD 62p) across the dialyzer in patients treated with postdilution online HDF as compared to HD [28]. Moreover, in this study, the degree of hemoconcentration correlated significantly with the drop in platelet numbers and the rise in the expression of CD62p. Considering platelet derived micro-particles, similar results were obtained patients treated with predilution and postdilution online HDF [27].

Summarizing, although it is highly likely that postdilution online HDF is less bio-incompatible than HD due to the more pronounced hemoconcentration and higher TMP, little information is available on this subject. Both platelet activation and coagulation (see Chap. 19) are most pronounced during postdilution online HDF. Due to the diluting effect of the infusion in predilution online HDF, its bio-incompatibility profile seems less prominent as compared to postdilution online HDF.

Financial/Economic Perspective

An often heard comment is that online HDF is more expensive than standard HD. Indeed, as argued above, starting up online HDF may mean extra investments in equipment, organization and training. However, once online HDF has become a routine treatment in a particular center, its costs appear comparable to those of HD with high flux dialyzers.

The CONTRAST investigators did a formal cost-effectiveness analysis and reported that online HDF was approximately 3 % more expensive than standard low-flux HD, based on 2009 cost levels. The extra costs were mainly caused by more frequent cultures of the dialysate and the more expensive disposables [29]. Since the frequency of testing has decreased considerably in recent years and disposables became cheaper, the costs of online HDF have decreased considerably. Indeed, recent studies showed that online HDF may be as cost-effective as high flux HD or even cheaper [30, 31].

Practical Perspective

Is HDF more difficult to perform than standard HD? If we accept the idea that a certain minimum dosage is necessary to obtain the benefits of HDF, it is clear that we need to focus on HDF with online production of substitution fluids. Key requirements for performing high volume postdilution HDF are mentioned in Table 25.1. Do these requirements mean any disadvantage of the treatment?

It is clear that the technical infrastructure needs to be such that water of adequate quality can be produced consistently and permanently. It is important to realize that

it is conceptually incorrect to demand different and stricter quality levels for the water treatment system when it is used for HDF than for the use of high flux membranes only. Standard HD using high flux membranes, which is presently preferred guide line based treatment, should actually be considered as "low dose" HDF, because back filtration of dialysate into the patient occurs [32, 33]. So, if one accepts that the use of high flux membranes is standard and that the same quality standards are necessary, one might as well choose for the treatment for which available evidence suggests that it is beneficial to the patients, i.e. online HDF. Technical staff responsible for the maintenance of the technical infrastructure needs to be aware of this situation. It seems appropriate to institute a platform/committee within the institution that is responsible for the monitoring and assurance that water of continuous adequate quality is produced. In such a committee the nephrologist, dialysis staff, hospital pharmacist and microbiologist and the technical department should be present or represented.

To ensure the achievement of high convection volume in clinical practice, the dialysis staff should be aware of the factors that determine the magnitude of the convection volume. Therefore, special training and constant inspiration are necessary, as was done in ESHOL [2]. So, indeed, extra investments in manpower and motivation are necessary when aiming for a permanent and uninterrupted delivery of high convection volumes in online HDF [32].

Effects on the coagulation system are discussed elsewhere. Online HDF may need 10–25 % more of heparin than regular HD treatment. Further, it is very well possible that handling of various medications during HDF differ from that during standard HD. Therefore, this subject is discussed in a separate chapter (Chap. 24).

Is HDF possible in all patients? An often heard comment on the fact that high volume is achieved in certain patients while not in others, is that this is a sign of selection bias. In other words, that patients with well performing vascular access are the "healthier" patients within the dialysis population. The CONTRAST investigators argued that in their study population there is no reason whatsoever to suggest that this idea is correct [34]. In fact the contrary. They argued that practice patterns rather than patient characteristics determine the level of achieved convection volumes [34]. How to achieve adequate convection volumes is discussed in much detail in Chap. 23.

Summary and Conclusions

Although the infusion of large volumes of online produced substitution volume may carry the risk of contamination, at present there is no concern about the microbiological safety of online filtration techniques, provided that state of the art water treatment systems, able to produce water of adequate quality, is used and its functioning is systematically monitored. With regard to other medical aspects, loss of albumin may be more pronounced during online filtration techniques as compared to conventional HD. Regarding bio-incompatibility, activation of platelets and

coagulation is more pronounced during online HDF, most likely due to the high hemoconcentration and TMP within the dialyzer. So far, no clear clinical side effects have been described, although data on potential side effects other than microbiological safety, are scarce.

Starting up an online HDF program may mean to set up a new infrastructure and an education plan, which, indeed, may be associated with some extra costs and efforts to stimulate and motivate the employees of the dialysis department. Thereafter, the costs of the maintenance phase appear more or less identical to a regular HD program using high flux membranes. Accepting the likelihood of its superiority, online HDF is probably cost effective.

Teaching Points

- An often heard concern is the microbiological safety of online HDF. Present evidence indicates that high volume online post-dilution HDF can be performed safely from a microbiological perspective on the condition that state of the art water treatment system able to produce water of adequate quality is used and its functioning is systematically monitored.
- High volume online post-dilution HDF may result in the unwanted removal of nutrients or other useful compounds. The relevance of this is unclear.
- High volume online post-dilution HDF is associated with activation of blood cells. The relevance of this is unclear.
- Starting up a high volume online post-dilution HDF program needs extra effort (and maybe costs). Effort and costs of the maintenance of a well running program are comparable to that of a program using high flux membranes.

References

1. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.
2. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
3. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
4. Mostovaya IM, Blankestijn PJ, Bots ML, Covic A, Davenport A, Grooteman MP, et al. Clinical evidence on hemodiafiltration: a systematic review and a meta-analysis. Semin Dial. 2014;27(2):119–27.
5. Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, et al. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. Am J Kidney Dis. 2014;63(6):954–67.

6. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2013;28(11):2859–74.
7. Wang AY, Ninomiya T, Al-Kahwa A, Perkovic V, Gallagher MP, Hawley C, et al. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. Am J Kidney Dis. 2014;63(6):968–78.
8. Penne EL, Visser L, van den Dorpel MA, van der Weerd NC, Mazairac AH, van Jaarsveld BC, et al. Microbiological quality and quality control of purified water and ultrapure dialysis fluids for online hemodiafiltration in routine clinical practice. Kidney Int. 2009;76(6):665–72.
9. Canaud B, Wizemann V, Pizzarelli F, Greenwood R, Schultze G, Weber C, et al. Cellular interleukin-1 receptor antagonist production in patients receiving on-line haemodiafiltration therapy. Nephrol Dial Transplant. 2001;16(11):2181–7.
10. Pizzarelli F, Maggiore Q. Clinical perspectives of on-line haemodiafiltration. Nephrol Dial Transplant. 1998;13 Suppl 5:34–7.
11. Vaslaki LR, Berta K, Major L, Weber V, Weber C, Wojke R, et al. On-line hemodiafiltration does not induce inflammatory response in end-stage renal disease patients: results from a multicenter cross-over study. Artif Organs. 2005;29(5):406–12.
12. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Mazairac AH, Penne EL, et al. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. Kidney Int. 2014;86(2):423–32.
13. Borrelli S, Minutolo R, De NL, Zamboli P, Iodice C, De PA, et al. Intradialytic changes of plasma amino acid levels: effect of hemodiafiltration with endogenous reinfusion versus acetate-free biofiltration. Blood Purif. 2010;30(3):166–71.
14. Combarnous F, Tetta C, Cellier CC, Wratten ML, De Custaud CT, et al. Albumin loss in on-line hemodiafiltration. Int J Artif Organs. 2002;25(3):203–9.
15. Masakane I, Esashi S, Igarashi H. Biocompatibility of predilution on-line hemodiafiltration. Blood Purif. 2013;35 Suppl 1:34–8.
16. Krieter DH, Hackl A, Rodriguez A, Chenine L, Moragues HL, Lemke HD, et al. Protein-bound uraemic toxin removal in haemodialysis and post-dilution haemodiafiltration. Nephrol Dial Transplant. 2010;25(1):212–8.
17. Fournier A, Birmele B, Francois M, Prat L, Halimi JM. Factors associated with albumin loss in post-dilution hemodiafiltration and nutritional consequences. Int J Artif Organs. 2015; 38(2):76–82.
18. Vega A, Quiroga B, Abad S, Aragoncillo I, Arroyo D, Panizo N, et al. Albumin leakage in online hemodiafiltration, more convective transport, more losses? Ther Apher Dial. 2015; 19(3):267–71.
19. Beerenhout CH, Luik AJ, Jeuken-Mertens SG, Bekers O, Menheere P, Hover L, et al. Predilution on-line haemofiltration vs low-flux haemodialysis: a randomized prospective study. Nephrol Dial Transplant. 2005;20(6):1155–63.
20. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Penne EL, Mazairac AH, et al. Clinical predictors of decline in nutritional parameters over time in ESRD. Clin J Am Soc Nephrol. 2014;9(2):318–25.
21. Cross J, Davenport A. Does online hemodiafiltration lead to reduction in trace elements and vitamins? Hemodial Int. 2011;15(4):509–14.
22. Fehrman-Ekholm I, Lotsander A, Logan K, Dunge D, Odar-Cederlof I, Kallner A. Concentrations of vitamin C, vitamin B12 and folic acid in patients treated with hemodialysis and on-line hemodiafiltration or hemofiltration. Scand J Urol Nephrol. 2008;42(1): 74–80.
23. Morena M, Cristol JP, Bosc JY, Tetta C, Forret G, Leger CL, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. Nephrol Dial Transplant. 2002;17(3):422–7.
24. Gonzalez-Diez B, Cavia M, Torres G, Abaigar P, Camarero V, Muniz P. The effects of 1-year treatment with a haemodiafiltration with on-line regeneration of ultrafiltrate (HFR) dialysis on

biomarkers of oxidative stress in patients with chronic renal failure. Mol Biol Rep. 2012;39(1):629–34.
25. Filiopoulos V, Hadjiyannakos D, Metaxaki P, Sideris V, Takouli L, Anogiati A, et al. Inflammation and oxidative stress in patients on hemodiafiltration. Am J Nephrol. 2008; 28(6):949–57.
26. Grooteman MP, Gritters M, Wauters IM, Schalkwijk CG, Stam F, Twisk J, et al. Patient characteristics rather than the type of dialyser predict the variability of endothelial derived surface molecules in chronic haemodialysis patients. Nephrol Dial Transplant. 2005;20(12):2751–8.
27. Sakurai K, Saito T, Yamauchi F, Asahi D, Hosoya H. Comparison of the effects of predilution and postdilution hemodiafiltration on neutrophils, lymphocytes and platelets. J Artif Organs. 2013;16(3):316–21.
28. Gritters-van den Oever M, Grooteman MP, Bartels PC, Blankestijn PJ, Bots ML, van den Dorpel MA, et al. Post-dilution haemodiafiltration and low-flux haemodialysis have dissimilar effects on platelets: a side study of CONTRAST. Nephrol Dial Transplant. 2009;24(11):3461–8.
29. Mazairac AH, Blankestijn PJ, Grooteman MP, Penne EL, van der Weerd NC, den Hoedt CH, et al. The cost-utility of haemodiafiltration versus haemodialysis in the Convective Transport Study. Nephrol Dial Transplant. 2013;28(7):1865–73.
30. Lebourg L, Amato S, Toledano D, Petitclerc T, Creput C. Online hemodiafiltration: is it really more expensive? Nephrol Ther. 2013;9(4):209–14.
31. Takura T, Kawanishi H, Minakuchi J, Nagake Y, Takahashi S. Cost-effectiveness analysis of on-line hemodiafiltration in Japan. Blood Purif. 2013;35 Suppl 1:85–9.
32. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28(3):542–50.
33. Blankestijn PJ. Has the time now come to more widely accept hemodiafiltration in the United States? J Am Soc Nephrol. 2013;24(3):332–4.
34. Chapdelaine I, Mostovaya IM, Blankestijn PJ, Bots ML, van den Dorpel MA, Levesque R, et al. Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration. Blood Purif. 2014;37(3):229–37.

Part V
Practical Issues

Chapter 23
Practical Guide to Performing High Volume Hemodiafiltration

Muriel P.C. Grooteman, Isabelle Chapdelaine, and Menso J. Nubé

Abstract The achievement of high volumes in online hemodiafiltration seems mandatory to obtain clinical benefit of the treatment. As of yet, evidence suggests that practice patterns rather than patient characteristics determine convection volume. The most important determinants of convection volume are treatment time, blood flow rate, and probably filtration fraction. Hematocrit plays a minor role. In this chapter, the treatment related factors are discussed in detail.

In order to achieve high convection volumes, a treatment time of at least 4 h, a blood flow rate of at least 300 ml/min (preferably up to 400 ml/min) and a filtration fraction up to 30 % is advisable. Knowledge of the characteristics of the dialysis machine used for optimization of the filtration fraction is helpful, as can be the case for automated machine settings. A central venous catheter is not a contra-indication to high volume HDF. Generally, the dose of anticoagulation is increased by 10–25 % as compared to standard HD. Finally, training of the dialysis staff and regular re-evaluation of convection volume are an essential part of the treatment optimization.

Keywords High volume hemodiafiltration • Treatment time • Blood flow • Convection flow • Substitution flow • Needle • Filtration fraction • Anticoagulation • Vascular access • Dialyzer

Introduction

From the three recently published large randomized clinical trials comparing online post-dilution hemodiafiltration (HDF) with hemodialysis (HD), a stepped relationship was demonstrated between convection volume and survival benefit [1–3]. Furthermore, in the only trial in which a convection volume of 22–23 L/treatment

M.P.C. Grooteman, MD, PhD (✉) • M.J. Nubé, MD, PhD
Department of Nephrology, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081 HV, The Netherlands
e-mail: mpc.grooteman@vumc.nl; mensonube@gmail.com

I. Chapdelaine, MD
Department of Nephrology, Hôpital du Sacré-Coeur de Montréal, Montréal, Québec, Canada

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_23

was achieved, a significant 30 % reduction in mortality was shown in the group of patients randomized to online post-dilution HDF [2]. Hence, convection volume appears to be of utmost relevance and one of the key parameters in the prescription of HDF [4].

In most smaller clinical trials and observational studies on post-dilution HDF, the convection volume ranged between 15 and 23 L per session. Convection volumes of <15 L per treatment are mainly observed in HDF with bags (so called *off-line* HDF), and will not be discussed in this chapter. In the CONTRAST study, the target convection volume of 24 L per treatment was achieved in only 22 % of the patients. Hence, just performing post-dilution online HDF does not automatically result in high convection volumes. In this chapter, not only determinants of convection volume will be discussed, but also several practical and technical issues when aiming for high volume HDF.

Determinants of Convection Volume in Post-dilution Online Hemodiafiltration

The variability in the magnitude of the convection volume in different studies is remarkable. The most obvious and intuitive explanation seems to be the assumption that high convection volumes can more easily be obtained in healthier patients with better vascular access. If so, the survival benefit of high volume HDF would be confounded by patient characteristics (dose targeting bias) [5]. This issue was investigated in CONTRAST. From this analysis, it appeared that treatment related parameters, such as blood flow and treatment time, rather than patient-related parameters including co-morbidity, vascular access, age and BMI, are the main determinants of the convection volume. Hematocrit and albumin played only a minor role [6, 7]. Moreover, this study clearly showed that patient characteristics did not differ between the lower, middle and highest tertile of achieved convection volume [6].

In another recent large observational study an association between treatment time and blood flow was also observed. From this study it appeared that the magnitude of the convection volume depended on the type of vascular access (fistula versus catheter), the filtration fraction (although this parameter was not assessed, but calculated from convection flow rate and blood flow rate), serum albumin and day of the week (Monday versus other days) [8]. The relative importance of these factors, however, was not reported in this study.

Chapdelaine et al. showed that the achieved convection volume varied roughly between 15 and 23 L in the participating CONTRAST centers. This was accompanied by large between-center differences in mean blood flow, treatment time and filtration fraction, as is shown in Fig. 23.1. In some facilities, *all* patients were treated with exactly the same blood flow rate, or with exactly the same treatment time, suggesting that center policy rather than patient characteristics influences the magnitude of the convection volume.

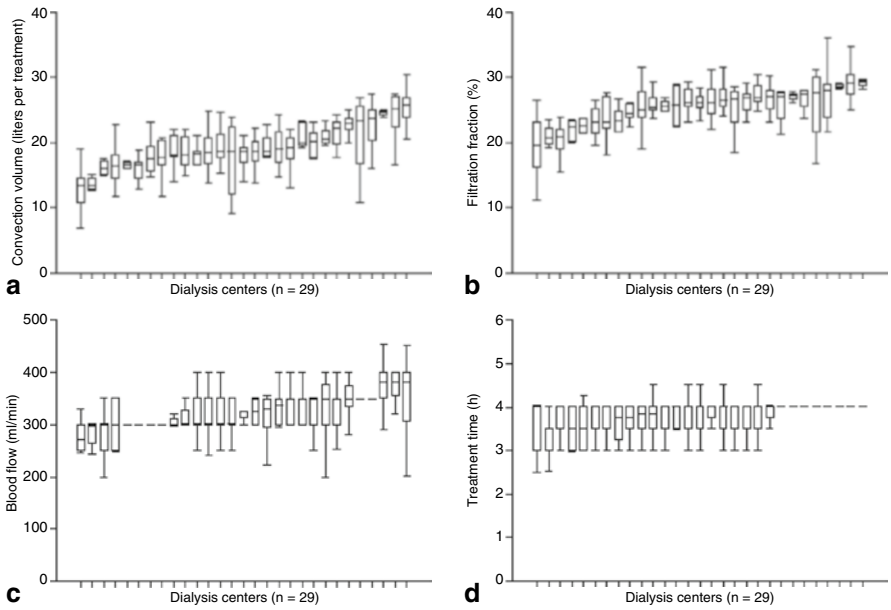


Fig. 23.1 Data from the 29 different centers participating in the CONTRAST study; *boxes* and *whiskers* represent median, 25th and 75th percentile, and range. Each box represents one single center. *Left upper panel*: achieved convection volume, *left lower panel*: set blood flow; *right upper panel*: filtration fraction (convective flow rate/blood flow rate); *right lower panel*: treatment time (Reprinted from Chapdelaine et al. [6]. With permission from Karger Publishers)

Definitions

The convection volume (or total ultrafiltration volume) consists of the substitution volume, the net ultrafiltration volume (difference between patient weight before and after dialysis), and the amount of extra fluids administered to (and removed from) the patient during the treatment. As the latter factor is usually modest and disregarded in clinical practice, it will not be taken into account in this chapter.

$$\begin{aligned} Convection\,volume(L) = {} & substitution\,volume(L) \\ & + net\,ultrafiltration\,volume(L) \end{aligned}$$

The convective flow rate is the convection volume divided by the treatment time.

$$\begin{aligned} Convective\,flow\,rate(ml/min, or\,L/h) = {} & convection\,volume(ml, or\,L) \\ & / treatment\,time(min, or\,h) \end{aligned}$$

Hence, the convection volume is determined by the convective flow rate and the treatment time:

$$Convection\,volume = convective\ flow\,rate * treatment\,time$$

Substitution volume is the amount of replacement fluid infused in the post-dilution mode (in case of post-dilution HDF) per treatment. Substitution flow rate is the amount of replacement fluid divided by treatment time:

$$Substitution\ flow\,rate\left(ml/min, or\ L/h\right) = substitution\,volume\left(ml, or\ L\right) / treatment\,time\left(min, or\ h\right)$$

Determinants of Convection Volume and Their Modulation

Treatment Time

Treatment time is tightly associated with, and one of the two main determinants of the achieved convection volume [6]. As convection volume is determined by the convective flow rate and treatment time, it is obvious that with increasing treatment time, the convection volume augments. A simple calculation was proposed by Penne et al. [9]. From Fig. 23.2, it is clear that an increase in treatment time from 3 to 4 h (+60 min), at a blood flow of 350 ml/min and a filtration fraction of 25 %, results in an increase in convection volume of 5.2 L. The same increase in time (+60 min) with a blood flow of 400 ml/min and a filtration fraction of 30 % results in a 7.2 L higher convection volume.

Probably, decisions on treatment time result from a complex interplay between practice patterns, patient preferences and characteristics, and commercial aspects [10]. Worldwide, treatment time varies significantly between different regions. According

FF (%)	20	21	22	23	24	25	26	27	28	29	30	31	32	33
Treatment time = 3 h 00 min														
Q_B = 300 mL/min	10.8	11.3	11.9	12.4	13.0	13.5	14.0	14.6	15.1	15.7	16.2	16.7	17.3	17.8
Q_B = 350 mL/min	12.6	13.2	13.9	14.5	15.1	15.8	16.4	17.0	17.6	18.3	18.9	19.5	20.2	20.8
Q_B = 400 mL/min	14.4	15.1	15.8	16.6	17.3	18.0	18.7	19.4	20.2	20.9	21.6	22.3	23.0	23.8
Treatment time = 3 h 30 min														
Q_B = 300 mL/min	12.6	13.2	13.9	14.5	15.1	15.8	16.4	17.0	17.6	18.3	18.9	19.5	20.2	20.8
Q_B = 350 mL/min	14.7	15.4	16.2	16.9	17.6	18.4	19.1	19.9	20.6	21.3	22.1	22.8	23.5	24.3
Q_B = 400 mL/min	16.8	17.6	18.5	19.3	20.2	21.0	21.8	22.7	23.5	24.4	25.2	26.0	26.9	27.7
Treatment time = 4 h 00 min														
Q_B = 300 mL/min	14.5	15.1	15.8	16.6	17.3	18.0	18.7	19.4	20.2	20.9	21.6	22.3	23.0	23.8
Q_B = 350 mL/min	16.8	17.6	18.5	19.3	20.2	21.0	21.8	22.7	23.5	24.4	25.2	26.0	26.9	27.7
Q_B = 400 mL/min	19.2	20.2	21.1	22.1	23.0	24.0	25.0	25.9	26.9	27.8	28.8	29.8	30.7	31.7

Percentages represent filtration fractions (i.e. convective flow rate divided by blood flow).
Convective volumes > 17 L per treatment are indicated in grey.
Values represent convective volumes in litres per treatment.
Q_B = dialyser blood flow, FF = filtration fraction.

Fig. 23.2 Convective volumes in post-dilution hemodiafiltration in relation to treatment time, blood flow rate and filtration fraction (Reprinted from Penne et al. [9]. With permission from Oxford University Press)

to DOPPS I-III data on >37,000 patients treated with HD three times a week, treatment time was shortest in the United States (214 min), and longest in Australia/New Zealand (256 min) [11]. Of note, in these regions treatment time increased in the period 1996–2008, possibly due to increasing awareness of its importance. More locally and confined in one time period, in CONTRAST, median treatment time varied from 3.5 to 4 h in participating dialysis centers. While in some centers treatment time varied between 2.5 and 4 h, in other centers all patients were treated for 4 h [6]. Hence, practice patterns indeed seem to play an important role in this respect.

Blood Flow

Besides treatment time, blood flow is a main determinant of convection volume, and hence, a high blood flow is a prerequisite for high volume HDF. The mean blood flow rates in CONTRAST and in the Turkish HDF study were 332 and 318 ml/min, respectively [1, 3], whereas in the Catalonian ESHOL study a markedly higher mean blood flow rate of 367–380 ml/min was achieved [2]. Mean blood flow differs widely between various geographic regions, being 400 ml/min (IQR 360–445) in the United States, 300 ml/min (IQR 300–340) in Europe and Australia/New Zealand, and 200 ml/min (IQR 180–200) in Japan [12]. In CONTRAST, the average blood flow rate differed widely between participating centers (275–375 ml/min) [6]. As can be deducted from Fig. 23.2, an increase in blood flow from 300 to 400 ml/min during a 4 h treatment with a filtration fraction of 25 %, results in an increase in convection volume of 6.0 L.

In clinical practice, a high blood flow did not result in hemodynamic instability [13], decreased cardiac function [14], or hemolysis, provided that the needle size is large enough [15].

Needle Size

Like blood flow and treatment time, the size of the needle used for puncture of the vascular access also varies greatly between dialysis centers and patients [16, 17]. Needle size is measured in gauge (G). This size indication is derived from standard scaling system originally designed for iron wire manufacture and has been approved by the International Organization for Standardization (ISO) of medical devices [18, 19]. The gauge of the needle refers to its *outer* diameter. Hence, the size of the lumen also depends on the thickness of the needle [20], as is shown in Fig. 23.3.

According to Poiseuille's law, the volumetric flow rate (Q) through a lumen is equal to:

$$Q = \frac{\pi * r^4 * |\Delta P|}{8\eta * L}$$

Where r = internal radius of the tube; $|\Delta P|$ = pressure difference between the two ends; η = dynamic fluid viscosity; L = tube length. Hence, a small increase in radius (r) translates into a relatively large increase in flow rate.

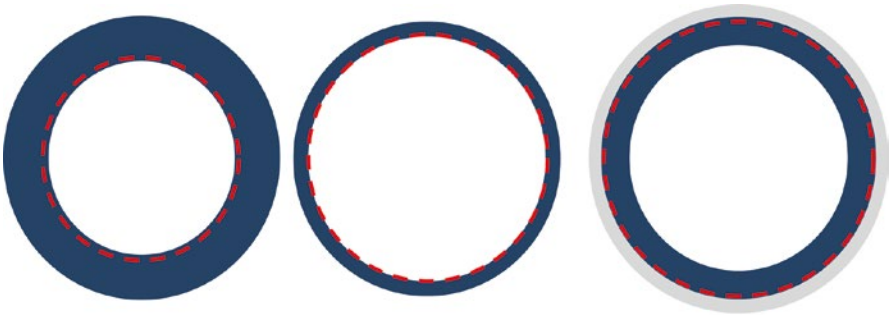


Fig. 23.3 All needles depicted (*blue circles*) have the same gauge (= outer diameter). The boundary of the lumen is indicated with the *red dotted line*, and differs between the different needles. *Left*: thick wall *(dark blue)*, small lumen (*white*); *middle*: thin wall, large lumen; *right*: plastic cannula (*light grey circle*), largest lumen after removal of the needle

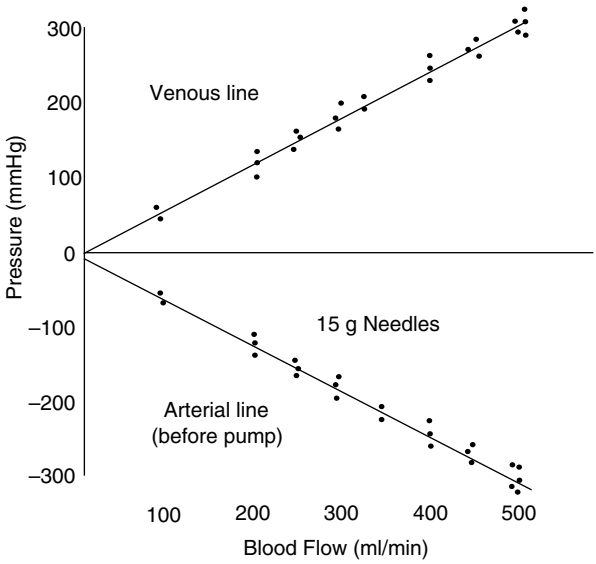


Fig. 23.4 Pressure values in the extracorporeal circuit at different blood flows (Reprinted from Ronco et al. [13]. With permission from Oxford University Press)

For example, a simple calculation using the abovementioned formula shows that just the switch from a 16 G needle, with a needle wall thickness of 0.229 mm and hence an inner diameter of 1.194 mm (r_1), to a 15 G needle, with the same thickness and an inner diameter of 1.372 mm (r_2), results in a $(r_2/r_1)^4 = 1.7$-fold increase in volumetric flow rate. At the same time, if the increase in flow rate is somewhat less, the pressure difference over the needle will be lower [13].

In an elegant study, it was shown that a change to a 1 G larger needle (mostly from 16 to 15 G) translated into higher delivered blood flow rates (from 379 to 402 ml/min) with a less negative arterial pressure and a lower venous pressure [21]. At maximized blood flow rates (arterial and venous pressure −250 and +250 mmHg, respectively), the increase in delivered blood flow was even higher (from 379 to 461 ml/min) after

Table 23.1 Dialysis cannula size in gauge and corresponding outer diameter

Gauge	Outer diameter (mm)
14	2.11
15	1.83
16	1.65
17	1.47
18	1.22

changing (increasing) the needle size with −1 G. The other way round, a nice link between arterial and venous pressures at different blood flow rates was shown when using the same needle size [13], Fig. 23.4.

Standard needle sizes range from 14 to 18 G (outer diameter 2.1 and 1.2 mm, respectively), see Table 23.1. The choice of needle size is often made by the nursing staff, and based on the type and vintage of the vascular access, bleeding tendency, or preference of the patients. Individual center practice patterns seem to play a pivotal role, as there is no evidence to support one practice over another [16]. In a survey in 171 European and South African dialysis centers, 61 % of shunts were cannulated with 15 G needles and 33 % with 16 G needles [17]. A clear relation was observed between needle size and blood flow rate, being <300 ml/min in >80 % of patients cannulated with a 17 G needle, and >400 ml/min in almost 50 % of patients cannulated with a 14 G needle. As especially shear stress may induce hemolysis [22], the combination of small needles and high blood flow should be avoided [23]. During dialysis with a 14 G needle and a blood flow rate of 500 ml/min both hemolysis and venous pressures were comparable to dialysis with a 17 G needle and a blood flow rate of 250 ml/min [15].

Unfortunately, there is little information on the influence of needle size on shunt outcome, which is possibly confounded by indication (smaller needles may be applied for fistulas or grafts at risk). In an observational study, the complication risk was similar with 14 G, 15 G or 16 G needles in both fistulas and grafts [24], whereas others found a slightly elevated risk of bleeding with 14 and 15 G needles as compared to 16 and 17 G [25].

In most vascular access guidelines, no specific gauge value is recommended, except for first cannulation [26]. In general, manufacturers advice needle size to match blood flow rate. For high volume online HDF, a blood flow of >350 ml/min and a needle size of 14 G or 15 G appears a rational choice.

Plastic Fistula Cannulae

At times, plastic fistula cannulae are used instead of steel needles, in order to allow some degree of movement to the patient. After puncture, the metal needle is removed from the covering cannula, which remains in situ. The gauge size listed on the product corresponds to the outer diameter of the central metal needle. Once this is removed, the lumen allowing for the flow of blood in the cannula is approximately 1 gauge larger than indicated on the packaging, see the right part of Fig. 23.3.

Set Versus Actual Blood Flow

As has been well established, the effective or actual blood flow rate is somewhat lower than the set blood flow rate. The difference is 5 % on average, but increases during dialysis treatment, with higher set blood flow rates and with smaller needles (higher Gauge value) [21, 27, 28]. Furthermore, the difference between actual and set blood flow depends on vascular access, being higher in central venous catheters than in arteriovenous (AV) fistulae [28, 29]. At a set blood flow rate of 348 ml/min, the actual blood flow was 2 % lower in AV fistula and 9 % lower in central venous catheters. Of note, these are mean values, with differences between set and actual blood flow up to 50 % in individual patients [29].

Single Needle Post-dilution Hemodiafiltration

In single needle HD, measured blood flow rates are approximately half of the rates during double needle dialysis [30], and blood flow rates should be doubled in order to achieve comparable processed blood volumes. Hence, the achievement of high convection volumes will be virtually impossible. Furthermore, as the blood flow is variable during single-needle dialysis, considerable variations in transmembrane pressure and filtration fraction will occur, probably hampering high filtration rates. Furthermore, even a high blood flow rate in single needle dialysis (500 ml/min for each pump) results in a lower dialysis dose as compared to double needle dialysis [31]. Hence, in order to achieve high volume HDF, single needle dialysis should be discouraged.

Blood Flow and Vascular Access

In order to achieve high blood flow rates, an adequate vascular access is mandatory. Guidelines do not recommend specific limits for access flow rate, but advise 'sufficient access blood flow for adequate hemodialysis' [32–34]. Huge differences exist in the distribution of vascular access type across countries and regions, with a prevalence of arteriovenous fistulae in Japan and the United States of 91 % and 47 %, respectively, and a prevalence of central venous catheters in Canada and Japan of 39 % and 2 %, respectively (in DOPPS III: 2005–2007) [35]. In vitro studies indicate that an access flow rate of 500 ml/min in a graft together with a blood flow rate of 400–500 ml/min in the extracorporeal circuit (ECC) lead to unacceptably high venous pressures [36].

Furthermore, in some studies an association was observed between blood flow rates, both at the high (>390 ml/min) and the low end of the spectrum (<312 ml/min), and access failure [12, 37]. As these data are observational, they do not allow conclusions on causality.

As for HDF, little information is available on this subject. In the Turkish HDF study, patients with central venous catheter were excluded [3]. In CONTRAST, 6 % of patients in the HDF group had a central venous catheter [1], and in ESHOL 7.5 % [2]. In CONTRAST, the achieved convection volume did not differ between patients with a central venous catheter and patients with a fistula or graft [6]. In a cross-over study in 63 patients, the convection volume was 8–9 % lower in patients with a central venous catheter as compared to a fistula. Nevertheless, convection volume in patients with catheters was 25–29 L during 4.7 h of treatment [38]. In none of these studies, however, information is available on the relation between access flow rate, blood flow rate in the extracorporeal circuit and convection volume. Nevertheless, to prevent recirculation, access flow should be markedly higher than blood flow in the ECC [37]. Taken together, when the blood flow rate in the extracorporeal circuit is at least 300 ml/min, high volume HDF is feasible, independent of the type of vascular access.

Filtration Fraction

Technically, the filtration fraction is defined as the ratio between the total ultrafiltration rate (or volume) and the plasma water flow rate (or volume):

$$FFpw = \left(Q_{conv} / Qpw\right) * 100$$

where FFpw = plasma water filtration fraction (%), Q_{conv} = convection flow rate (ml/min or L/h), and Qpw = (actual) plasma water flow rate (ml/min or L/h). The plasma water flow rate is defined as:

$$Qpw = Qb * \left(1 - Ht\right) * \left(1 - 0.0107\,TP\right)$$

Where Qpw = plasma water flow rate (ml/min or L/h), Qb = (actual) blood flow rate (ml/min or L/h), Ht = hematocrit and TP = total protein concentration in plasma (g/dL). According to the literature, in post-dilution HDF the FFpw can amount to 50 % [39]. For practical purposes however, it is much more convenient to use the blood flow rate instead of the plasma water flow rate, as the blood flow rate is readily available at the bed side [4]. Thus, the filtration fraction is defined as:

$$FF = \left(Q_{conv} / Qb\right) * 100$$

where FF = filtration fraction (%), Q_{conv} = convective flow rate, and Qb = (actual) blood flow rate.

The convective flow rate is determined by the sum of the substitution rate and intradialytic weight loss or net ultrafiltration.

Table 23.2 Variation of plasma water filtration fraction at given filtration fractions (based on bloodflow) and hematocrit at dialyzer inlet

Filtration fraction of bloodflow (%)	Hematocrit at dialyzer inlet	Corresponding plasma water filtration fraction (FFpw, %)	Estimated hematocrit at dialyzer outlet
25	0.25	36	0.33
25	0.30	39	0.40
25	0.35	42	0.47
30	0.25	43	0.36
30	0.30	46	0.43
30	0.35	50	0.50

Dialyzer outlet is before infusion port of substitution fluid. For simplicity, hematocrit values do not take the influence of time into account and total plasma protein remains stable at 7 g/dL

$$Q_{conv} = Q_{subs} + Q_{netUF}$$

At a higher filtration fraction, more plasma water is extracted from the blood and convection volume increases. As the substitution fluid is administered *after* the dialyzer in post-dilution HDF, hemoconcentration increases along the dialyzer capillaries, which may result in clotting, altered membrane performance, and increased filter entrance pressure (and hence alarms) [40].

It is important to realize that there are a few caveats when using the blood flow rate as a surrogate for plasma water flow rate. First, for a stable FF as calculated by the blood flow rate, the plasma water filtration fraction and resulting hemoconcentration can vary significantly due to variations in hematocrit (Table 23.2), and plasma protein content.

Second, as discussed before, the actual blood flow may be lower than the set blood flow. Hence, the actual filtration fraction will be somewhat higher than the filtration fraction estimated by the set blood flow. If, for example, the actual blood flow is 12.5 % lower than a set blood flow of 400 ml/min (i.e. 350 ml/min), the actual filtration fraction will be 28.6 % instead of 25 %.

Third, online HDF is a dynamic treatment. Several variables may change over time, such as net ultrafiltration rate (e.g. by individualized ultrafiltration profiles), protein deposition and micro-clotting within the dialyzer [41], and hemoconcentration due to net ultrafiltration. Hence, a high filtration fraction may be tolerated at the start of the session but not during the course of the treatment.

Substitution ratio and filtration fraction: Usually, treatment time, blood flow rate and net ultrafiltration volume are pre-set parameters. Indeed, in clinical practice, the desired weight loss of the patient is an important parameter and requires a distinct prescription, apart from the total convection volume. However, none of the dialysis systems currently on the market allows the setting of filtration fraction as a separate treatment parameter, and in order to target a certain convection volume, there is only one more parameter to prescribe:

1. Substitution ratio, or

2. Substitution flow rate, or
3. Target substitution volume

It is important to realize that the abovementioned target parameters based on substitution (and not convection) flow or ratio do not take net UF into account, although this can be a significant part of the total convection volume.

For example, in a patient with a desired intradialytic weight loss of 4 kg, a target substitution volume of 24 L equals to a convection volume of 28 L. If this patient is treated for 4 h with an actual blood flow of 400 ml/min, a substitution ratio of 25 % equals to a filtration fraction of 29 %; and a substitution flow rate of 100 ml/min translates into a convection flow rate of 117 ml/min.

When using an UF profile, these parameters do not remain steady throughout treatment: UF is usually highest at the start of the treatment, and so will be filtration fraction. If the same patient is starting at a net UF rate of 1,500 ml/h for the first hour, convection flow rate will be 125 ml/min and, with a substitution ratio of 25 %, the filtration fraction will amount to 31 % at that particular moment.

In most studies, filtration fraction is not assessed as such, but calculated from blood flow rate and convection flow rate [6, 8]. When doing this, a wide variation was shown in the median filtration fraction per participating center in CONTRAST (19–28 %, Fig. 23.1). Hence, although filtration fraction as such does not seem to be a practical parameter to set, increasing the convective flow rate or convection volume for a certain blood flow rate or blood volume seems rational, taking the achieved filtration fraction into account.

Automated Machine Settings

Prescribing HDF based on a substitution target (volume, rate or ratio) will lead to pressure alarms when one tries to manually optimize convection volume [42]. Indeed, the calculated convective flow rate will be more or less attainable, depending on the permeability of the dialyzer for plasma water (Kuf) and the transmembrane pressure (TMP) [43], which is mostly determined by the filtration fraction [40].

Therefore, automated machine settings have been developed in order to make treatment less complicated and less operator-dependent. For example, when the substitution flow rate was guided by a predefined range of the transmembrane pressures, convection volumes could be increased by 20–50 % [42, 44], and when an automatic stepwise increase in transmembrane pressure was allowed, convection volumes could even be increased up to 90 % [42]. The latter method resulted in a filtration fraction of 30 % [45], and a clear increase in alarm-free sessions [44]. Another approach is to adapt the substitution flow rate automatically to changes in blood viscosity within the dialyzer, based on transmembrane pressure assessment and pressure transmitted by the peristaltic blood pump [8, 38].

It is crucial to realize that automated machine settings try to optimize the filtration fraction at the lowest possible occurrence of machine alarms, but do not control the two main determinants of convection volume, namely treatment time and blood flow rate.

Anticoagulation

Both platelet activation and coagulation activity are increased during online post-dilution HDF, as compared to HD. Its cause is multifactorial and results most probably from a combination of greater hemoconcentration and shear stress within the dialyzer, and, depending on the degree of protein-binding, removal of anticoagulant medication. Only a few studies have addressed this subject. Gritters et al. found a markedly increased upregulation of the platelet surface marker CD62b during online post-dilution HDF [46], while Klingel et al. observed higher thrombin-antithrombin (TAT) complexes and D-dimer levels during pre-dilution hemo(dia) filtration, despite similar anti Xa levels [47]. In this study, patients were anticoagulated with enoxaparin (a low molecular weight heparin LMWH). By contrast, in comparison with HD, Sombolos et al. found reduced levels of anti-Xa activity after enoxaparin administration during online post-dilution HDF [48]. In clinical practice, the dose of the prescribed anticoagulant, either unfractionated heparin or LMWH was 10–25 % higher in patients treated with online post-dilution HDF than in HD patients [3, 49]. For further reading see Chap. 15.

Dialyzers

The hydraulic characteristics of a dialyzer are determined by the material of the membrane, the characteristics of the capillaries and the design of the dialyzer itself. According to Poiseuille's law, both the length and the internal radius of the capillaries determine the pressure drop over the dialyzer [50].

Little information is available on the performance of different dialyzers in online post-dilution HDF. In CONTRAST, dialyzers with a surface area between 1.7 and 2.2 m^2, an ultrafiltration (UF) coefficient between 56 and 85 ml/mmHg/h, a capillary lumen diameter between 185 and 215 μm and capillary length between 225 and 280 mm were applied. Despite these highly dissimilar characteristics between the various dialyzers, the achieved convection volumes were rather similar. Of note, however, as these data are observational by nature and the dialyzers were clustered in the participating centers, local practice patterns may have influenced these results considerably [6]. In a cross over study in 18 patients, 4 different dialyzers were tested with constant dialysis parameters. The dialyzer surface area varied from 1.8 to 2.2 m [2], the UF coefficient from 63 to 85 ml/mmHg/h, the lumen diameter from 200 to 215 μm and capillary length from 200 to 286 mm. As

expected, the highest convection volumes and filtration fractions were achieved by a dialyzer with the largest surface area, a high UF coefficient of 75 ml/mmHg/h, a wide capillary lumen diameter of 210 μm and a rather short capillary length of 200 mm [45]. Hence, it appears rational to choose a dialyzer presenting a smart combination of features minimizing pressure (wide capillary lumen and short fiber length) while optimizing filtration surface (large surface area). At this point it should be mentioned, however, that high convection volumes (up to 30 L) were also found using dialyzers with a capillary diameter of 185 μm and a 1.4 m^2 surface area [38, 51]. Therefore, further research on this topic is urgently warranted. For further reading see Chap. 4.

Practical Advice

In conclusion, the magnitude of the convection volume is determined mainly by blood flow rate and treatment time. In daily practice, both these parameters depend to a large extent on local habits and treatment patterns. Hence, in order to achieve high convection volumes, first the blood flow rate (>300 ml/min, ideal around 400 ml/min) and treatment time (≥4 h) should be optimized. Thereafter, filtration fraction should be increased (possibly to around 30 %), being aware of the target parameter used by the dialysis machine. An automated mode for the optimization of filtration fraction can be of help. Finally, training of the team, constant awareness and re-evaluation of the treatment and treatment goals at a regular basis are of utmost importance.

Teaching Points

- The main determinants of convection volume are treatment time and blood flow rate
- To obtain high convection volumes, optimize treatment time (at least 4 h), blood flow (up to 400 ml/min) and filtration fraction (up to 30 %)
- For an optimal blood flow, use a 14 G or 15 G needle, avoid single needle cannulation, consider discrepancies between set and actual blood flows
- Know the characteristics of the dialysis machine used for optimization of the filtration fraction
- Increase the coagulation dose of standard HD by 10–25 %
- Use a dialyzer with a large membrane surface area (>2 m^2), short capillaries, a high K_{UF} (>55 ml/mmHg/h) and an appropriate capillary diameter (>200 μm)
- Training of the dialysis staff and regular re-evaluation of convection volume goals is mandatory

References

1. Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
2. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
3. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28:192–202.
4. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28:542–50.
5. Greene T, Daugirdas J, Depner T, et al. Association of achieved dialysis dose with mortality in the hemodialysis study: an example of "dose-targeting bias". J Am Soc Nephrol. 2005; 16:3371–80.
6. Chapdelaine I, Mostovaya IM, Blankestijn PJ, et al. Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration. Blood Purif. 2014;37:229–37.
7. Penne EL, van der Weerd NC, Bots ML, et al. Patient- and treatment-related determinants of convective volume in post-dilution haemodiafiltration in clinical practice. Nephrol Dial Transplant. 2009;24:3493–9.
8. Marcelli D, Scholz C, Ponce P, et al. High-volume postdilution hemodiafiltration is a feasible option in routine clinical practice. Artif Organs. 2014;39(2):142–9.
9. Penne EL, van Berkel T, van der Weerd NC, Grooteman MP, Blankestijn PJ. Optimizing haemodiafiltration: tools, strategy and remaining questions. Nephrol Dial Transplant. 2009;24: 3579–81.
10. Daugirdas JT. Dialysis time, survival, and dose-targeting bias. Kidney Int. 2013;83:9–13.
11. Tentori F, Zhang J, Li Y, et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2012;27:4180–8.
12. Asano M, Thumma J, Oguchi K, et al. Vascular access care and treatment practices associated with outcomes of arteriovenous fistula: international comparisons from the Dialysis Outcomes and Practice Patterns Study. Nephron Clin Pract. 2013;124:23–30.
13. Ronco C, Feriani M, Chiaramonte S, et al. Impact of high blood flows on vascular stability in haemodialysis. Nephrol Dial Transplant. 1990;5 Suppl 1:109–14.
14. Alfurayh O, Galal O, Sobh M, et al. The effect of extracorporeal high blood flow rate on left ventricular function during hemodialysis – an echocardiographic study. Clin Cardiol. 1993;16:791–5.
15. Techert F, Techert S, Woo L, Beck W, Lebsanft H, Wizemann V. High blood flow rates with adjustment of needle diameter do not increase hemolysis during hemodialysis treatment. J Vasc Access. 2007;8:252–7.
16. Chapdelaine I, de Roij van Zuijdewijn CL, Mostovaya IM, et al. Optimization of the convection volume in online post-dilution haemodiafiltration: practical and technical issues. Clin Kidney J. 2015;8:191–8.
17. Gauly A, Parisotto MT, Skinder A, et al. Vascular access cannulation in hemodialysis patients – a survey of current practice and its relation to dialysis dose. J Vasc Access. 2011;12:358–64.
18. Iserson KV. The origins of the gauge system for medical equipment. J Emerg Med. 1987;5:45–8.
19. ISO 9626. Stainless steel needle tubing for the manufacture of medical devices. Amendment 1. 1–2. Geneva: International Organisation for Standardization; 2001. Ref Type: Generic.
20. Ahn W, Bahk JH, Lim YJ. The "Gauge" system for the medical use. Anesth Analg. 2002;95:1125.
21. Mehta HK, Deabreu D, McDougall JG, Goldstein MB. Correction of discrepancy between prescribed and actual blood flow rates in chronic hemodialysis patients with use of larger gauge needles. Am J Kidney Dis. 2002;39:1231–5.

22. Polaschegg HD. Red blood cell damage from extracorporeal circulation in hemodialysis. Semin Dial. 2009;22:524–31.
23. De Wachter DS, Verdonck PR, De Vos JY, Hombrouckx RO. Blood trauma in plastic haemodialysis cannulae. Int J Artif Organs. 1997;20:366–70.
24. van Loon MM, Kessels AG, van der Sande FM, Tordoir JH. Cannulation practice patterns in haemodialysis vascular access: predictors for unsuccessful cannulation. J Ren Care. 2009;35:82–9.
25. Hasbargen JA, Weaver DT, Hasbargen BJ. The effect of needle gauge on recirculation, venous pressure and bleeding from puncture sites. Clin Nephrol. 1995;44:322–4.
26. Vascular Access 2006 Work Group. Clinical practice guidelines for vascular access. Am J Kidney Dis. 2006;48 Suppl 1: S176–247.
27. Kimata N, Wakayama K, Okano K, et al. Study of discrepancies between recorded and actual blood flow in hemodialysis patients. ASAIO J. 2013;59:617–21.
28. Sands J, Glidden D, Jacavage W, Jones B. Difference between delivered and prescribed blood flow in hemodialysis. ASAIO J. 1996;42:M717–9.
29. Canaud B, Leray-Moragues H, Kerkeni N, Bosc JY, Martin K. Effective flow performances and dialysis doses delivered with permanent catheters: a 24-month comparative study of permanent catheters versus arterio-venous vascular accesses. Nephrol Dial Transplant. 2002; 17:1286–92.
30. Huang SH, Shah S, Thomson BK, Laporte S, Filler G, Lindsay RM. What is single needle cannulation hemodialysis: is it adequate? Blood Purif. 2014;38:13–7.
31. Rostoker G, Griuncelli M, Loridon C, Bourlet T, Welsch K, Benmaadi A. Improving the efficiency of short-term single-needle hemodialysis. Ren Fail. 2009;31:261–6.
32. Huijbregts HJ, Blankestijn PJ. Dialysis access – guidelines for current practice. Eur J Vasc Endovasc Surg. 2006;31:284–7.
33. Navuluri R, Regalado S. The KDOQI 2006 vascular access update and fistula first program synopsis. Semin Interv Radiol. 2009;26:122–4.
34. Tordoir J, Canaud B, Haage P, et al. EBPG on vascular access. Nephrol Dial Transplant. 2007;22 Suppl 2:ii88–117.
35. Ethier J, Mendelssohn DC, Elder SJ, et al. Vascular access use and outcomes: an international perspective from the Dialysis Outcomes and Practice Patterns Study. Nephrol Dial Transplant. 2008;23:3219–26.
36. Van Tricht I, De Wachter D, Tordoir J, Vanhercke D, Verdonck P. Experimental analysis of the hemodynamics in punctured vascular access grafts. ASAIO J. 2005;51:352–9.
37. Ponce P, Marcelli D, Scholz C, et al. Does the extracorporeal blood flow affect survival of the arteriovenous vascular access? Hemodial Int. 2015;19(2):314–22.
38. Maduell F, Rodriguez N, Sahdala L, et al. Impact of the 5008 monitor software update on total convective volume. Nefrologia. 2014;34:599–604.
39. Colussi G, Frattini G. Quantitative analysis of convective dose in hemofiltration and hemodiafiltration: "predilution" vs. "postdilution" reinfusion. Hemodial Int. 2007;11:76–85.
40. Pedrini LA, De Cristofaro V, Pagliari B, Sama F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000;58:2155–65.
41. Huang Z, Gao D, Letteri JJ, Clark WR. Blood-membrane interactions during dialysis. Semin Dial. 2009;22:623–8.
42. Teatini U, Steckiph D, Romei LG. Evaluation of a new online hemodiafiltration mode with automated pressure control of convection. Blood Purif. 2011;31:259–67.
43. Joyeux V, Sijpkens Y, Haddj-Elmrabet A, Bijvoet AJ, Nilsson LG. Optimized convective transport with automated pressure control in on-line postdilution hemodiafiltration. Int J Artif Organs. 2008;31:928–36.
44. Panichi V, De Ferrari G, Saffioti S, et al. Divert to ULTRA: differences in infused volumes and clearance in two on-line hemodiafiltration treatments. Int J Artif Organs. 2012;35:435–43.
45. Albalate RM, Perez GR, de Sequera OP, et al. Clinical application of Ultracontrol(R): infusion volume and use with different dialyzers. Nefrologia. 2011;31:683–9.
46. Gritters-van den Oever M, Grooteman MP, Bartels PC, et al. Post-dilution haemodiafiltration and low-flux haemodialysis have dissimilar effects on platelets: a side study of CONTRAST. Nephrol Dial Transplant. 2009;24:3461–8.

47. Klingel R, Schaefer M, Schwarting A, et al. Comparative analysis of procoagulatory activity of haemodialysis, haemofiltration and haemodiafiltration with a polysulfone membrane (APS) and with different modes of enoxaparin anticoagulation. Nephrol Dial Transplant. 2004;19:164–70.
48. Sombolos KI, Fragia TK, Gionanlis LC, et al. The anticoagulant activity of enoxaparin sodium during on-line hemodiafiltration and conventional hemodialysis. Hemodial Int. 2009; 13:43–7.
49. de Roij van Zuijdewijn C, Nube MJ, Blankestijn PJ, et al. The prescribed dose of low molecular weight heparin increases after assigning patients to hemodiafiltration (HDF) treatment. J Am Soc Nephrol 2014;25 (abstract supplement):292A.
50. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58:809–17.
51. Maduell F, Arias-Guillen M, Fontsere N, et al. Elimination of large uremic toxins by a dialyzer specifically designed for high-volume convective therapies. Blood Purif. 2014;37:125–30.

Chapter 24
Medication and Hemodiafiltration

Anthe S. Zandvliet, Daniel J. Touw, and E. Lars Penne

Abstract The amount of drug clearance during online hemodiafiltration (HDF) is determined by (1) the pharmacokinetic properties of a drug defined by its absorption, distribution, metabolism and elimination (ADME) characteristics, (2) dialysis characteristics, including membrane properties, treatment time and blood-, dialysate- and ultrafiltration flow rates, and (3) patient factors. For several drugs, especially those within the middle molecular weight range, with low protein binding and neutrally or positively charged, clearance may be substantially higher during HDF as compared to conventional low flux hemodialysis. Based on drug characteristics, the expected additional effect of a high ultrafiltration rate, as indicated by a high convection volume, can be estimated. This is shown for anticoagulants, antibiotics and antiviral drugs. For drugs with an expected additional effect of convection and for drugs with a narrow therapeutic window, therapeutic drug monitoring may be advisable. Comparative data from clinical studies is scarce. Hence, for an individual patient it may be relevant to calculate the total amount of a drug excreted during an HDF session. This can easily be performed in routine clinical practice and may guide the clinician to estimate the dose of the drug needed for suppletion upon completion of HDF treatment. Examples are provided how to calculate drug suppletion after HDF. Collectively, this chapter is intended as a guidance to optimize pharmacotherapy in online HDF patients.

Keywords Antibiotics • Anticoagulants • Clearance • Convection • Diffusion • Drug • Dialysis • Hemodiafiltration • Intoxication • Pharmacokinetics

A.S. Zandvliet, PharmD, PhD (✉)
Department of Clinical Pharmacology and Pharmacy, VU Medical Center,
Boelelaan 1118, Amsterdam 1081 HZ, The Netherlands
e-mail: Anthe.Zandvliet@vumc.nl

D.J. Touw, PharmD, PhD
Department of Clinical Pharmacy and Pharmacology, University of Groningen,
University Medical Center Groningen, Groningen, The Netherlands

E.L. Penne, MD, PhD
Department of Internal Medicine, Medical Center Alkmaar, Alkmaar, The Netherlands

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_24

Introduction

Online hemodiafiltration (HDF) is increasingly used in clinical practice as a routine intermittent dialysis modality. During HDF diffusive and convective solute removal are combined to optimize clearance of uremic waste products. Three large randomized controlled trials have suggested improved clinical outcomes after long term HDF as compared to low-flux or high flux hemodialysis (HD), as long as large convection volumes are applied [1–3].

It is well recognized that renal impairment and dialysis can substantially affect the pharmacokinetics of a drug. Dosing adjustments are usually either an alteration of the administered dose or an alteration of the dosing interval. Not only drugs that are primarily cleared by the kidneys require dosage adjustment. Drugs that are predominantly metabolized by the liver may also be affected by dialysis, as long as metabolites are active (or toxic), water soluble and protein binding is low. There is only limited evidence whether additional dose adjustments are required when solute removal is increased during HDF as compared to HD. Potentially, increased clearance by HDF may lead to underdosing of several drugs.

In this chapter, factors that determine drug clearance in intermittent HD and HDF patients are presented. These factors comprise drug characteristics, dialysis characteristics and patient factors. Published studies supporting dosing recommendations in online HDF as compared to conventional HD are reviewed, focusing on anticoagulants and antibiotics. Continuous dialysis therapies used for acute kidney injury are beyond the scope of this chapter.

In many pharmacotherapeutic areas, clinical pharmacokinetic studies in HDF patients are lacking, possibly since online HDF is a rather new development in dialysis practice. Hence, especially for drugs with a narrow therapeutic window, it may be relevant to determine the total amount of a drug excreted during an HDF session, to estimate the dose needed for suppletion after the dialysis session. In this chapter these calculations are explained and recommendations for therapeutic drug monitoring (TDM) are provided.

Collectively, this chapter is intended as a guidance to optimize pharmacotherapy in online HDF patients.

Determinants of Drug Clearance in HDF Patients

The clearance of a drug during renal replacement therapy (RRT) depends on dialysis characteristics, drug characteristics and patient factors. Together, these determinants guide the physician about the need for dose adjustments to optimize pharmacotherapy in patients treated with online HDF. Dosing regimens suitable for patients with normal renal function may result in drug accumulation due to renal impairment. Conversely, dosing regimens suitable for patients treated with conventional HD may result in undertreatment when a patient is treated with online HDF. A solid understanding of the various determinants affecting drug clearance by dialysis may help to

judge the risk of over- and undertreatment, which is especially relevant when clinical studies are lacking and/or when therapeutic drug monitoring is not possible.

Dialysis Characteristics

Drug clearance by dialysis is determined by (1) treatment duration, (2) treatment frequency and (3) treatment intensity.

Increasing treatment time, e.g. from 4 to 8 h as in nocturnal dialysis or increasing treatment frequency, as in short daily dialysis, results in significantly increased removal of drugs with a low or middle molecular weight. Clearance of drugs with high protein binding also increases, although to a lesser extent [4–7]. Necessary drug dosing adjustments that are required for these dialysis modalities are beyond the scope of this chapter.

Dialysis intensity is dependent on the amount of diffusion and convection during treatment [8]. Diffusion is based on a concentration gradient between the blood and dialysate compartment in the dialyzer, and is dependent on the blood flow rate, dialysate flow rate and dialyzer specifications [9]. Diffusion is the predominant form of solute removal in conventional low flux HD. Diffusion is very efficacious for removal of drugs with low molecular weight, low protein binding and low volume of distribution. When drugs become larger, molecule charge is becoming more important, as well as dialyzer specifications. During HDF, convection is added to diffusion to optimize solute removal. Convective transport is based on a pressure gradient between the blood and dialysate compartment in the dialyzer, resulting in a flux (or ultrafiltration [UF]) across the membrane. The amount of drug clearance by convection is directly related to the magnitude of the convection volume. The convection volume is dependent on blood flow rate, dialysis treatment time and dialyzer specifications [10]. Molecule size is of minor importance, as long as the molecule fits through the pores of the membrane. Of the drugs with high protein binding, only the free fraction is cleared by dialysis.

Dialyzer Specifications

Current dialyzers may differ from each other with respect to membrane material, hollow fiber dimensions, membrane pore-related characteristics, surface area, and non-membrane related determinants of dialyzer performance, e.g. sterilization process or fiber packing [11]. The dialyzer specifications that are most relevant for drug clearance in clinical practice are the total surface area and the UF coefficient (K_{UF}) [12]. The total surface area of the dialyzer is the maximal area available for blood contact and is directly related to the clearance of small molecular weight solutes. The K_{UF} is defined as the amount of fluid per hour transferred through the membrane per mmHg pressure gradient across the membrane. Membranes with high K_{UF} (high-flux dialyzers; K_{UF} >20 ml/min/mmHg) have large pores that are capable of

passing larger molecules, as compared to membranes with lower K_{UF} (low-flux dialyzers; $K_{UF} \leq 20$ ml/min/mmHg). For drug clearance during dialysis this implies that larger molecules (arbitrarily defined a molecular weight >500 kD) can only be removed with high-flux dialyzers. HDF is exclusively performed with high-flux dialyzers. Recently, high-efficiency high-flux dialyzers have been developed to further optimize middle molecular weight removal during HDF. The main benefit of these filters was observed with a molecular weight ranging from 17 to 33 kD [13]. Since the vast majority of therapeutic drugs have a molecular weight below 1 kD, it is unlikely that these high efficiency high-flux membranes will have therapeutic consequences for drug dosing and suppletion.

Notably, the flux of the dialyzers has increased over the years due to technical advances. Practical dosing advise for dialysis patients as mentioned in textbooks often originate from studies in which traditional dialyzers were used with very low K_{UF}. Following such advice may lead to underdosing, especially when patients are treated with high-flux HD or HDF. Switching patients from low-flux HD to high-flux HD or online HDF should trigger a reassessment of dosing regimens, especially for chronically applied drugs with a narrow therapeutic index. Failure to individualize and optimize the dosing regimen may result in suboptimal treatment. This was illustrated by a case of a patient treated with valproic acid who experienced seizures, following a switch from conventional low flux HD to online HDF. Increased drug removal had resulted in subtherapeutic valproic acid exposure after online HDF [14].

Adsorption

During dialysis treatment, a protein layer is formed on the dialyzer membrane [15]. On the one hand, the adsorbed protein layer on the membrane may negatively affect solute removal during dialysis, since the permeability of the membrane decreases. On the other hand, adsorption can contribute to the total clearance of a drug, especially if it has a high protein binding. The amount of adsorption largely depends on the membrane material. Only limited data is available on the importance of adsorption for therapeutic drug clearance during dialysis [16].

Drug Characteristics

The potential increment of drug removal by convection during online HDF can be assessed based on molecular weight, protein binding, volume of distribution and charge. Compounds with low protein binding and a low volume of distribution are typically efficiently eliminated by dialysis. An additional effect on drug clearance due to convection during online HDF can be anticipated for compounds with a relatively large molecular weight (provided that protein binding is low and volume of distribution is small). In contrast, for low molecular weight drugs, the removal during RRT is typically not largely impacted by convection, but mostly driven by diffusion.

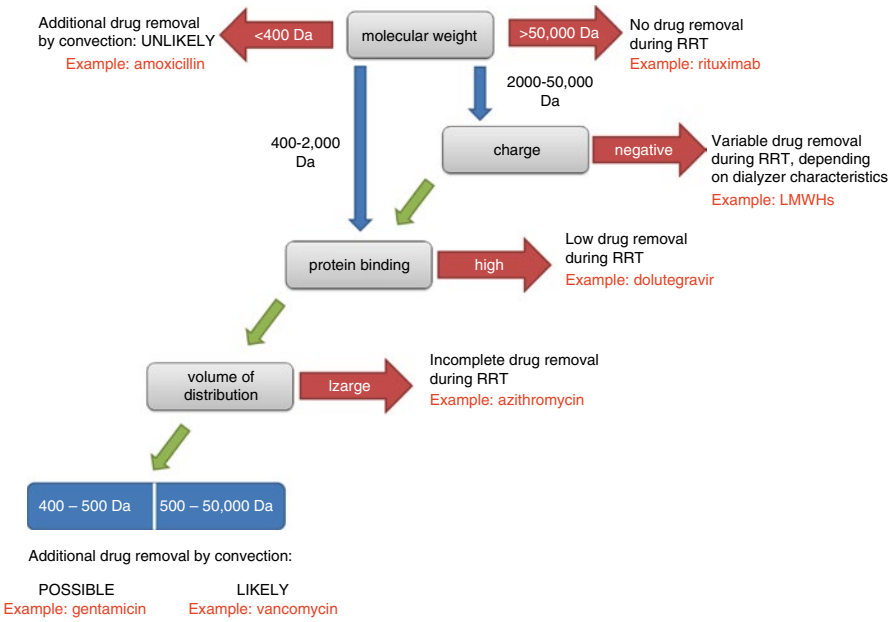


Fig. 24.1 Algorithm to assess the potential increment of drug removal by convection

A systematic evaluation of drug characteristics can be conducted to assess the potential increment of drug removal by convection. In Fig. 24.1, an algorithm is presented which can help to determine if increased drug removal seems likely. For drugs with a narrow therapeutic range, where online HDF may result in increased drug clearance, TDM could be considered to prevent undertreatment.

Patient Factors

Pharmacokinetic processes, i.e. absorption, distribution, metabolism and elimination (ADME) may be altered in patients with renal impairment. Obviously, renal elimination is reduced. In addition, other pharmacokinetic processes may also differ from patients with normal renal function.

Absorption may be decreased due to uremic neuropathy or concomitant medication and intestinal edema. The volume of distribution could be increased in case of sepsis, chronic fluid overload, or due to reduced protein binding (resulting in a larger amount of free drug which may distribute into the tissues leading to a decrease in plasma concentration). For example, for valproic acid it has been shown that protein binding was lower in uremic conditions due to drug displacement by uremic toxins [17]. Protein binding may also be reduced due to hypoalbuminemia. Free fraction of protein bound drugs will be higher in patients with hypoalbuminemia. Although it has been shown that albumin loss in the dialysate is significantly greater during HDF as compared to HD [18], albumin levels are similar in HDF and HD patients [2, 19].

The impairment of renal clearance may for some drugs be limited to reduced glomerular filtration, but may for other drugs also comprise disruption of active tubular secretion (e.g. piperacillin, oseltamivir) or reabsorption (e.g. levetiracetam, lithium). In patients with renal dysfunction, not only renal elimination may be reduced, but hepatic metabolism may also be altered. Oxidative pathways for certain drugs may be accelerated, and other metabolic functions such as acetylation, hydrolysis, and reduction may be reduced. These concepts are elucidated into more detail by Swan et al. [20]. Notably, not only the parent drug but also relevant active/toxic metabolites should be taken into consideration. For instance, only trace amounts of oseltamivir are eliminated unchanged in urine, but since the active metabolite of oseltamivir is renally eliminated, dose adjustments are indicated in patients with renal impairment.

In patients with end stage renal disease, RRT contributes to drug clearance. In addition, residual kidney function can be an important contributor to drug clearance [21]. The presence of residual kidney function may especially affect drugs that are actively secreted (piperacillin, oseltamivir) or reabsorbed (lithium, levetiracetam) by the tubulus. Although oseltamivir is eliminated during RRT, dialysis is not equally efficient as active tubular secretion [22]. For oseltamivir, drug clearance could be highly variable between dialysis patients depending on the amount of residual kidney function. For removal of endogenous compounds, preservation of residual kidney function is also considered of high importance and may even outweigh the effect of intensifying dialysis treatment [23]. It is unfortunate that residual renal function is often an exclusion criterion in farmacokinetic studies in HD patients [24].

Calculation of Drug Suppletion After Online HDF

In an individual patient, it may be relevant to determine the total amount of a drug excreted during an HDF session. This may influence the dose needed for suppletion of a drug with a narrow therapeutic window upon completion of HDF treatment. The total amount excreted may be assessed by concentration measurements before and after the dialyzer (pre and post dialyzer samples) collected at various time points during the HDF session (Table 24.1).

Table 24.1 Samples to be collected during HDF to assess total amount of drug excreted

Sample	Location	Time		Specimen
C_{art} start	Pre dialyzer	0 %	5 min after start of HDF	Plasma/serum[ǂ]
C_{ven} start	Post dialyzer			
C_{art} 50 %	Pre dialyzer	50 %	Half-way HDF session	
C_{art} end	Pre dialyzer	100 %	5 min before end of HDF	
C_{ven} end	Post dialyzer			

C_{art} is the drug concentration in the arterial line of the extracorporeal circuit, C_{ven} is the drug concentration in the venous line. [ǂ] Samples to be collected

Pre and post dialyzer concentrations can be used to calculate drug clearance (CL) during HDF, using Eqs. 24.1a and 24.1b. Plasma clearance is a composite of:

- Plasma flow rate $\quad Qplasma = Qblood \times \left(1 - \text{hematocrit} / 100\right)$, and
- Extraction ratio $\left(\text{ER}\right) \quad \text{ER} = \left(C_{art} - C_{ven}\right) / C_{art}$

where Q is flow rate, C_{art} is the concentration of the drug in the arterial line of the extracorporeal circuit, and C_{ven} in the venous line.

Ideally, when flow rates are maintained at constant values throughout the time course of an HDF session, drug clearance in mL/min at the start and end of the session should be similar.

The total amount of excreted drug during the HDF session can be derived using Eq. 24.2 and is a composite of:

- Plasma clearance (mL/min)
- HDF duration (min)
- Plasma concentration (mg/mL)

Plasma concentration is not constant during the time course of a HDF session. A conservative estimate of the total amount of drug excreted can be obtained using the pre dialyzer concentration at the end of the HDF session (C_{art} end) as illustrated in Eq. 24.3a. Alternatively, the pre dialyzer concentration when the HDF session is half-way completed (C_{art} 50 %) could be used, which will result in a reasonable approximation of the total amount of drug excreted (Eq. 24.3b). For drugs with one compartment pharmacokinetic characteristics (i.e. no substantial tissue distribution, fast redistribution processes and no rebound after completion of HDF), Eq. 24.3c can be used which represents an integration of drug clearance over the HDF time interval resulting in an exact calculation of the total amount of drug excreted.

Drug concentrations are typically measured in plasma or serum (Eq. 24.1a). In selected cases, e.g. drugs highly bound to or incorporated in erythrocytes, whole blood bioanalytical assays may be used (Eq. 24.1b).

$$CLplasma = Qblood \times \left(1 - hematocrit / 100\right) \times \left(\left(C_{art} - C_{ven}\right) / C_{art}\right) \quad (24.1a)$$

$$CLblood = Qblood \times \left(\left(C_{art} - C_{ven}\right) / C_{art}\right) \quad (24.1b)$$

$$Amount\ \ excreted = clearance * duration * plasma\ \ concentration \quad (24.2)$$

$$Amount\ excreted\left(conservative\ \ estimate\right) = clearance * duration * C_{art}\ \ end \quad (24.3a)$$

$$Amount\ \ excreted\left(reasonable\ \ estimate\right) = clearance * duration * C_{art}\ \ 50\% \quad (24.3b)$$

$$Amount\ \ excreted\left(exact\ \ estimate^{\#\$}\right) = clearance * duration * \left(C_{art}\ \ start - C_{art}\ \ end\right) / ln\left(C_{art}\ \ start / C_{art}\ \ end\right) \quad (24.3c)$$

Exact estimate for drugs with one compartmental pharmacokinetics; this equation may result in an overestimation of the amount excreted for drugs with slow redistribution from tissue compartments.

As an example, this strategy may be used to determine the dose of lithium to be suppleted after HD or HDF. For instance, a lithium clearance of 130 mL/min (calculated from Eq. 24.1) and a C_{art} end of 0.35 mmol/l would result in conservative estimate of lithium removal of 10.9 mmol (equivalent to 400 mg lithiumcarbonate) to during a 4-h dialysis session. An alternative method to assess the lithium removal would be to determine the lithium concentration in dialysate as illustrated by Schmidt et al. [25]. However, dialysate concentration measurement seems to have low feasibility in HDF due to large dialysate volumes and consequently low drug concentrations at risk of falling below the lower limit of quantification.

Relevant Drug Groups

Therapeutic drug classes that are typically used in dialysis patients have been selected for a more in-depth evaluation in this chapter:

- Erythropoietin
- Vitamins
- Anticoagulants
- Antimicrobial agents

Especially the anticoagulants and antimicrobial drugs typically have a narrow therapeutic range, while their clearance during online HDF has typically not been studied in clinical trials. In this section, we aim to provide tools to support risk assessments when patients are treated with online HDF. This may help to judge whether therapeutic drug monitoring (TDM) based on serum concentration measurements is indicated to optimize the dosing regimen in an individual patient.

Erythropoietin Stimulating Agents (ESA)

Most dialysis patients suffer from chronic anemia. As extensively described in Chap. 12, renal anemia is a multifactorial process driven by reduced erythropoietin (EPO) production by the kidneys, EPO resistance of the bone marrow, decreased red blood cell life span and disturbed iron homeostasis. Generally, anemia in dialysis patients can be well controlled with erythropoietin stimulating agents (ESA) and iron suppletion. However, in some patients high ESA doses are required, which is associated with adverse clinical outcome [26].

Apart from chronic inflammation and malnutrition, the accumulation of uremic toxins has been implicated in the pathogenesis of ESA resistance. Various uremic toxins may directly inhibit erythropoiesis and EPO synthesis. Also for red cell life span, that is reduced independent of mechanical damage during hemodialysis

treatment, potential uremic toxins have been identified that may promote early phagocytosis of red blood cells [27].

Increasing the dialysis dose (as measured by Kt/V_{urea}) does improve ESA resistance as long as Kt/V <1.4 [28]. However, data are conflicting whether an increase in convective transport, as occurring in online HDF, can further improve ESA resistance. All studies on this topic are reviewed in Chap. 12. Two out of three large HDF trials, CONTRAST and ESHOL, did not show any difference in ESA resistance between HDF and HD patients, whereas a decrease in ESA resistance was observed in the Turkish HDF study [2, 3, 29]. As of yet, there is insufficient data to advise a patient to switch from conventional HD to high efficiency HDF in order to improve ESA resistance.

Vitamins

The great majority of dialysis patients is taking vitamin suppletion to compensate for losses of water soluble (B and C) vitamins during dialysis treatment and prevent vitamin deficiency. Without suppletion, deficiency of vitamin C (molecular mass 176D, negligible protein binding) occurs in approximately one third of HD patients [30]. Dialytic clearance of vitamin C is high, predominantly by diffusion [31]. It has been shown that vitamin C concentrations were not lower in HDF as compared to HD patients. Cobalamin (Vit B12; molecular mass 1346D) is a larger molecule but is highly protein bound. Hence dialytic removal is limited and is also not different for HDF and HD [32]. Dialytic removal of thiamin (Vit B1, molecular mass 265D), rivoflavin (Vit B2, 376D) and folate (B9, molecular mass 441D) is low due to a large volume of distribution. Pyridoxine (Vit B6; molecular mass 169D) is cleared by HD, however, the molecule is too small to expect differences in clearance between HD and HDF [33]. Taken together, there is no evidence that vitamin suppletion in dialysis patients should be adjusted based on treatment modality.

Anticoagulants

Anticoagulants are prescribed for prophylaxis or treatment of venous, arterial or extracorporeal thrombosis. Several main categories can be defined: coumarins, unfractionated heparin (UFH), low molecular weight heparines (LMWH), pentasaccharide inhibitors of factor Xa, direct factor Xa inhibitors, direct thrombin inhibitors. In Table 24.2, the typical application of the various anticoagulants are outlined.

For arterial thrombosis, coumarins or direct factor Xa/thrombin inhibitors are typically used. For peri-operative bridging, for treatment of venous thrombosis and for anticoagulation of the extracorporeal circuit, heparins (UFH or LMWH) are indicated. For patients with heparin induced thrombocytopenia (HIT) and consequently a contraindication for heparins, fondaparinux/danaparoid/argatroban can be applied. Since anticoagulants have a narrow therapeutic range, dose titration based on INR/aPTT/anti Xa/ACT is typically recommended in RRT.

Table 24.2 Typical application of main categories anticoagulants in patients with renal insufficiency

	Coumarins	Unfractionated heparin (UFH)	Low molecular weight heparines (LMWH)	Indirect factor Xa inhibitors	Direct thrombin inhibitors	Direct factor Xa inhibitors
Example drugs	Warfarin Acenocourmarol Phenprocoumon		Tinzaparin Nadroparin Dalteparin Enoxaparin	Fondaparinux (pentasaccharide) Danaparoid (heparinoid)	Dabigatran Bivalirudin Argatroban	Rivaroxaban Apixaban
Prophylaxis arterial thrombosis	INR guided	Rarely used	Rarely used	Rarely used	Severe renal insufficiency (dabigatran): contraindication	Severe renal insufficiency: contraindication
Peri-operative	Peri-operative: contraindication	Peri-operative: aPTT guided	Peri-operative: dose reduction, anti Xa guided	Peri-operative: indication HIT, anti Xa guided	Peri-operative: contraindication	Peri-operative: contraindication
Prophylaxis venous thrombosis	INR guided	Rarely used	Low dose	Rarely used	Rarely used	Rarely used
Treatment venous thrombosis	INR guided	aPTT guided	Severe renal insufficiency: dose reduction, anti Xa guided dose titration	Indication HIT (danaparoid), anti Xa guided	Indication HIT (argatroban/bivalirudin), aPTT/ACT guided dose titration	Severe renal insufficiency: contraindication
Extracorporeal thrombosis	Not indicated	Inspection of clot formation in air trap/aPTT guided dose titration	Inspection of clot formation in air trap/anti Xa guided dose titration	Indication HIT (danaparoid and fondaparinux), inspection of clot formation in air trap/anti Xa guided dose titration	Indication HIT (argatroban/bivalirudin), inspection of clot formation in air trap aPTT/ACT guided dose titration	Not indicated

Recommendation HDF versus HD	No difference in treatment strategy for HDF versus HD	No difference in treatment strategy for HDF versus HD In clinical practice: dose with HDF 10 % higher [2]	No difference in treatment strategy for HDF versus HD Clearance during HDF and HD dependent on dialyzer membrane [34]	Danaparoid: no data in HDF, no difference in treatment strategy for HDF versus HD Fondaparinux: dose finding in HDF patients suggests starting dose of 0.3 mg/kg followed by anti Xa guided dose titration [36]	No difference in treatment strategy for HDF versus HD	No difference in treatment strategy for HDF versus HD
			In clinical practice: dose with HDF 10 % higher [35]			

Coumarins

Coumarins are largely hepatically eliminated, highly protein bound and most likely not susceptible for removal during HDF. In patients with renal dysfunction, accumulating waste products may compete with coumarins for protein binding. This results in increased hepatic clearance (unless saturation occurs) resulting in lower total concentrations and not necessarily in different effects. Regular INR monitoring in this patient population is warranted. Coumarins are not indicated for anticoagulation of the extracorporeal circuit. However, in patients treated with a coumarin, the heparin (UFH/LMWH) starting dose for extracorporeal anticoagulation may be reduced to 50 % of normal [37]. See below.

Low Molecular Weight Heparines (LMWH)

During HD, the coagulation system is activated. Therefore, to prevent clot formation in the extracorporeal circuit (ECC), anticoagulation is required. During HDF, both thrombin formation, as measured by thrombin–antithrombin-III complexes (TAT), and platelet activation, as measured by an upregulation of the cell surface marker CD62p, are more pronounced than during HD [10, 38, 39]. These phenomena are attributed not only to the high transmembrane pressure during HDF, but also to the prominent hemoconcentration within the dialyzer. As a result, prevention of clot formation within the ECC in HDF patients may require higher LMWH doses than HD patients. Moreover, as LMWHs have a mean molecular weight of 4,000–5,000 Da and therefore qualify as middle molecular weight molecules, the convective component of HDF treatment may result in an incremental clearance as compared to HD. Indeed, in CONTRAST the LMWH dose was approximately 10 % higher in HDF patients as compared to HD [35]. Thus, while it is generally assumed that an anti Xa activity of 0.4 IU/l is required to minimize the risk of coagulation in HD [40], the treatment target may in fact be higher in HDF patients. In clinical studies, however, the clearance of enoxaparin and dalteparin appeared rather low during both HD and HDF, which is explained by the negative charge of LMWHs and their resistance to adsorption onto the negative surface of dialyzer membranes [38, 41]. Hence, membrane characteristics, especially its electrical charge, rather than the dialysis mode appear to be important determinants of LMWH removal during both HD and HDF [34]. For dalteparin, a starting dose of 60 IU/kg appeared adequate in HDF patients [42]. See also Chap. 15. The increased activation of the coagulation system in HDF may motivate future monitoring of TAT in addition to anti Xa activity.

Unfractionated Heparin (UFH)

Unfractionated heparin molecules (MW 12,000–15,000 Da) are more negatively charged than LMWH. As most dialyzer membranes are also negatively charged, heparin removal during HDF is probably lower than suggested by its molecular size. As a result,

UFH dose during this type of treatment may be lower than anticipated. By contrast, due to the highly unphysiological conditions within the dialyzer, as aforementioned, treatment with HDF may require higher doses. Ultimately, the UFH dose in HDF is determined by the balance between its relatively low adsorptive tendency at the one hand and a higher propensity for clot formation at the other. In the Turkish HDF Study, the unfractionated heparin dose was ~25 % higher in the HDF group when compared with HD patients [2]. Heparin dosing is titrated based on aPTT and on visual inspection of clot formation in the air trap chamber, which is indifferent between HDF and HD.

Indirect Factor Xa Inhibitors

For patients with heparin induced thrombocytopenia (HIT), fondaparinux can be considered as an alternative. Fondaparinux is a middle molecular weight pentasaccharide, which carries a lower negative charge than the LMWH enoxaparin. As expected, the clearance of fondaparinux is higher during high flux HD as compared to low flux HD [43]. The optimal starting dose was determined to be 0.3 mg/kg followed by anti Xa guided dose titration [36]. Another alternative for patients with HIT is danaparoid. Substantial experience with danaparoid for ECC anticoagulation is available [Summary of Product Characteristics (SPC), danaparoid]. No clinical data in HDF patients have been published. Anti Xa guided dose titration is indicated for HD as well as HDF.

Direct Thrombin and Direct Factor Xa Inhibitors

For bivalirudin and argatroban no clinical data in HDF patients have been published. Both thrombin inhibitors may be used in HIT for ECC anticoagulation using aPTT or ACT for dose titration. No marked differences between HD and HDF are anticipated.

The NOACs (non-vitamin K antagonist oral anticoagulants) are contraindicated for anticoagulation in patients with severe renal insufficiency [24]. Removal by HD or HDF is not very efficient due to high protein binding and a large volume of distribution resulting in a rebound phenomenon [44].

For ECC anticoagulation in HD citrate can be used as an alternative for UFH/LMWH. In HDF, however, insufficient evidence for its safe application is currently available [45].

Antimicrobial Agents

The various categories of antimicrobial drugs contain a wide variety of drug characteristics. Table 24.3 lists the most relevant drug characteristics including molecular weight, protein binding and volume of distribution. While data on conventional HD are available for a selection of antimicrobial drugs, removal by online HDF has

Table 24.3 Drug characteristics and anticipated impact of convective transport for a selection of antimicrobial agents

Category	Drug	Molecular weight (Da)	Volume of distribution (L/kg)	Protein binding (%)	Renal clearance (%)	Removal by intermittent HD session	Additional effect of convection	Ref
Antibiotics								
Tetracyclines	Doxycycline	462.4	0.7	>90	33–45	–	Unlikely	
	Tetracycline	444.4	>0.7	20–65	55–60	± (10 %)	Possibly	
Penicillines	Amoxicillin	365.4	0.3	20	60	+	Unlikely	
	Clavulanic acid	199.2	0.3	25	40	+	Unlikely	
	Benzylpenicillin	334.4	0.3–0.42	60	60–90	+	Unlikely	
	Flucloxacillin	453.9	0.13	95	66–76 active secretion	–	Unlikely	
	Piperacillin	517.6	0.18–0.3	20–30	60–80 active secretion	+ (30–40 %)	Likely	
	Tazobactam	300.3	0.18–0.33	20–30	80 active secretion	+ (30–40 %)	Unlikely	
Cephalosporins	Ceftazidim	637.7	0.28–0.4	<10	80–90	+	Likely	
	Cefuroxime	424.4	0.13–1.8	50	85–90	+	Possibly	
	Cefotaxime	455.5	0.15–0.55	40	40–60	+	Possibly	
	Ceftriaxone	554.6	0.12–0.18	85–95	40–60	–	Possibly	
Carbapenems	Imipenem	317.4	0.23	20	20–70	+ (55 %)	Unlikely	[55]
	Cilastatin	380.4	0.22	40	75	+ (63 %)	Unlikely	[55]
	Meropenem	437.5	0.35	2	70	+	Possibly	
	Doripenem	420.5	0.2	9	>70	+	Possibly	[46]
Sulfonamides and trimethoprim	Trimethoprim	290.3	1–2.2	45	40–60	+	Unlikely	
	Sulfamethoxazole	253.3	0.28–0.38	70	15–30	+	Unlikely	
	Sulfadiazine	250.3	0.29	20–55	80	++	Unlikely	

Macrolides, lincosamides	Azithromycin	785	31.1	12–52	6–12	–	Unlikely	
	Clarithromycin	748	2–4	80	15–40	±	Possibly	
	Clindamycin	425.0	0.6–1.2	>90	10	–	Unlikely	
	Erythromycin	733.9	0.6–1.2	70–95	2–15	–	Possibly	
Aminoglycosides	Tobramycin	467.5	0.25	<5	90	+	Possibly	
	Gentamicin	477.6	0.3	0–30	90	+	Possibly	[51]
	Amikacin	585.6	0.22–0.29	<20	94–98	+	Likely	
	Streptomycin	581.6	0.26	34–35	29–89	+	Likely	
	Netilmicin	475.6	0.16–0.3	<5	80	+	Likely	[50]
Quinolones	Ciprofloxacin	331.3	2.5	20–40	40–70	±	Unlikely	
	Levofloxacin	361.4	1.1–1.5	30–40	>85	±	Unlikely	
	Moxifloxacin	401.4	2	30–50	19	±	Unlikely	
	Norfloxacin	319.3	2.5–3.1	14	30	±	Unlikely	
Glycopeptides	Teicoplanin	1,875–1,891	0.94–1.4	90	>97	±	Likely	[52]
	Vancomycin	1449.3	0.47–1.1	10–50	80–90	±	Likely	
Other antibiotics	Colistin	~1,748 (colisti-methate sodium)	0.09–0.34	55	80	+	Likely	[56]
	Metronidazol	171.2	0.7–1.5	10–20	20	+	Unlikely	
	Linezolid	337.3	0.6	31	30	+ (30 %)	Unlikely	

(continued)

Table 24.3 (continued)

Category	Drug	Molecular weight (Da)	Volume of distribution (L/kg)	Protein binding (%)	Renal clearance (%)	Removal by intermittent HD session	Additional effect of convection	Ref
Antimycotics								
Triazoles	Fluconazole	306.3	0.65–0.7	11–12	80	+ (50 %)	Unlikely	
	Itraconazole	705.6	10	99.8	<0.03	–	Unlikely	
	Voriconazole	349.3	4.6	58	<2	± (13 %)	Unlikely	[47]
	Posaconazole	700.8	1,774 l	>98	<0.2	–	Unlikely	
Other antimycotics	Amphotericin B	924.1	2–4	>90	2–5	–	Unlikely	
	Flucytosine	129.1	0.65–0.91	2–4	90	+	Unlikely	
	Caspofungin	1093.3	0.15	97	1.4	–	Possibly	
	Anidulafungin	1140.2	30–50 l	>99	<1	–	Unlikely	
Antimycobacterial antibiotics								
	Ethambutol	277.2	1.6–3.2	20–30	50	+	Unlikely	
	Isoniazid	137.1	0.75	0	4–32	+	Unlikely	
	Rifampicine	822.9	0.64–0.66	80	15–30	–	Possibly	
	Pyrazinamide	123.1	0.75–1.3	10	4	+	Unlikely	
Anti (retro) viral drugs								
Nucleoside reverse transcriptase inhibitors NRTIs	Zidovudine	267.2	1.6	34–38	8–25	±	Unlikely	
	Lamivudine	229.3	1.3	<36	70	+	Unlikely	
	Didanosine	236.2	1	<5	20	+	Unlikely	
	Stavudine	224.2	0.5	<1	40	+	Unlikely	
	Abacavir	286.3	0.8	49	2	±	Unlikely	
	Emtricitabine	247.2	1.1–1.7	<4	86	+ (30 %)	Unlikely	
	Entecavir	295.3	Large	13	75	± (13 %)	Unlikely	

Nucleotide reverse transcriptase inhibitors NtRTIs	Tenofovir	287.2	0.8	0.7–7.2	Oral: 32	± (10 %)	Unlikely	
	Adefovir dipivoxil	501.5	0.4	<4	45	+ (35 %)	Possibly	
	Cidofovir	279.2	0.3–0.8	<6	80–100	+ (52–75 %)	Unlikely	
Non-nucleoside reverse transcriptase inhibitors NNRTIs	Efavirenz	315.7	2–4	>99	<1	–	Unlikely	
	Nevirapine	266.3	1.12–1.3	60	<3	+	Unlikely	
	Etravirine	435.3	422 l (apparent Vd)	>99	1.2	–	Unlikely	SPC Intelence
	Rilpivirine	366.4	152 l (apparent Vd)	>99	<5	–	Unlikely	FDA assess-ment report
Protease inhibitors	Saquinavir	670.8	10	98	<4	–	Unlikely	
	Ritonavir	720.9	0.4	98–99	3.5	–	Unlikely	
	Indinavir	613.8	14	60	10.4	–	Unlikely	
	Nelfinavir	567.8	2–7	>98	1–2	–	Unlikely	
	Amprenavir	505.6	6	90	<3	–	Unlikely	
	Lopinavir	628.8	0.5	98–99	2.2	–	Unlikely	
	Atazanavir	704.9	88 l (apparent Vd)	86	7	±	Possibly	[57]
	Fosamprenavir	585.6	6	90	<1	–	Unlikely	
	Tipranavir	602.7	7.7–10.2 l	>99.9	0.5	–	Unlikely	
	Darunavir	547.7	29–181 l	95	7.7	±	Possibly	
	Simeprevir	749.9	No data	>99	<1	–	Unlikely	
	Boceprevir	519.7	772 l	75	3	–	Unlikely	SPC Victrelis; [58]
	Telaprevir	679.8	252 l	59–76	<1	±	Possibly	SPC Incivo

(continued)

Table 24.3 (continued)

Category	Drug	Molecular weight (Da)	Volume of distribution (L/kg)	Protein binding (%)	Renal clearance (%)	Removal by intermittent HD session	Additional effect of convection	Ref
Integrase inhibitors	Raltegravir	444.4	No data	83	9	+	Possibly	[48]
	Elvitegravir	447.8	No data	98–99	<7	–	Unlikely	SPC Vitekta
	Dolutegravir	419.4	No data	>99	<1	–	Unlikely	SPC Tivicay
DNA polymerase inhibitors	Aciclovir	225.2	0.7	9–33	40–70	+	Unlikely	
	Ganciclovir	255.2	0.54–0.87	<2	85–95	+	Unlikely	
	Foscarnet	300	0.4–0.6	14–17	85	+	Unlikely	
Neuraminidase inhibitors	Oseltamivir	312.4	0.3–0.4	42 (3 active metabolite)	99 (active metabolite)	+ active secretion	Unlikely	[22]

Based on data from [59]

SPC summary of product characteristics

typically not been investigated. Therefore, based on the drug characteristics and based on the algorithm presented in this chapter, we have assessed the likelihood of convection to increase drug clearance during RRT.

Small Molecules <500 Da

Since conventional low-flux HD results in an effective removal of small molecules with a low volume of distribution and low protein binding, including the sulfonamides, carbapenems and the majority of the penicillins, these drugs should be supplemented after completion of a dialysis session. Due to the small molecular weight, the amount of drug that is removed is determined by the blood flow rate, dialysate flow rate, dialyzer characteristics and treatment duration, while the addition of convection, as in high-flux HD and HDF, is unlikely to substantially increase their clearance. Nevertheless, from a pharmacokinetic study on doripenem (carbapenem group) in patients with sepsis, who were treated with high volume HDF, it appeared that a substantial amount was eliminated, in this special case most probably by a combination of diffusion and an extremely high amount of convective transport [46]. Although comparative studies between HD and HDF are lacking, based on the small molecular weight, in general, large differences in the clearance between the two modalities are not to be anticipated.

A large volume of distribution may result in limited drug removal during dialysis. For instance, voriconazole (349.3 Da) has a distribution volume of 4.6 L/kg. Hafner et al. conducted a clinical trial and indeed demonstrated that only a limited proportion of the administered dose was removed during a 6-h treatment with HD (12.7 %) or online HDF (13.1 %) [47]. High protein binding explains the limited clearance of the new integrase inhibitors during RRT. Especially for elvitegravir and dolutegravir, protein binding is high (>98 %). Hence suppletion after RRT is not indicated. For raltegravir, protein binding is lower (~83 %) allowing the removal of free drug during HD, as observed by Moltó et al. [48]. Due to the low molecular weight, no increased removal during online HDF should be anticipated.

Larger Molecules >500 Da

As opposed to the other penicillins, piperacillin has a relatively high molecular weight of 517.6 Da. Therefore, the addition of convection to diffusion might increase its clearance. Indeed, piperacillin clearance was larger during online HDF as compared to historical data from patients who were treated with conventional HD [49]. Increased drug removal during online HDF is also anticipated for ceftazidim (637.7 Da), colistin (1,748 Da as colistimethate sodium), the aminoglycosides and the glycopeptides.

The aminoglycoside netilmicin was studied by Basile et al. in 1985, comparing low volume HDF with standard low flux HD. From this study it appeared that a markedly increased clearance was observed by the implementation of a high flux filter [50]. Sombolos et al. observed increased removal of the aminoglycoside gentamicin in a small study comparing online HDF with low flux HD [51]. Given their relatively large molecular weight, similar effects of convective transport can be anticipated for the other aminoglycosides, especially for amikacin and streptomycin.

For the glycopeptides teicoplanin and vancomycin, differences between conventional low flux HD and online HDF may be mostly relevant as substantial evidence exists that substantial drug removal occurs during high flux HD [52, 53]. Unfortunately, however, for online HDF only limited clinical data are available. Sombolos et al. observed subtherapeutic vancomycin levels in online HDF patients, even when anuric, after treatment with 15 mg/kg during the last hour of a 4-h session [54]. In coherence with the drug characteristics, these findings suggest that teicoplanin and vancomycin may be more efficiently removed by online HDF. Therapeutic drug monitoring is warranted to mitigate the risk of subtherapeutic exposure.

Considering antiviral drugs, especially the protease inhibitors have a relatively large molecular weight and could therefore be candidates for increased clearance by convection. However, the majority of the protease inhibitors are highly protein bound and/or have a large volume of distribution. Based on the overview presented in Table 24.2, for most antiviral drugs, convective transport unlikely substantially contributes to drug removal during RRT.

Conclusions

Unfortunately, only a few clinical pharmacokinetic studies in patients undergoing online HDF have been published. In this chapter, an algorithm for drug characteristics is presented. Convection typically increases drug clearance during renal replacement therapy for substances with large molecular weight (>500 Da), low to moderate protein binding and a small volume of distribution. This information can help to assess the potential impact of convective transport on drug removal during online HDF and may support the decision whether therapeutic drug monitoring (TDM) is required to optimize a patient's dosing regimen. Especially for drugs with a narrow therapeutic range, concentration measurements may be indicated. Based on drug concentrations in samples collected pre and post filter at several time points, the amount of drug removal during an online HDF session can be calculated. Particularly for the glycopeptides teicoplanin and vancomycin, TDM is strongly recommended to prevent undertreatment.

References

1. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.

2. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
3. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
4. Fagugli RM, De Smet R, Buoncristiani U, Lameire N, Vanholder R. Behavior of non-protein-bound and protein-bound uremic solutes during daily hemodialysis. Am J Kidney Dis. 2002;40(2):339–47.
5. Eloot S, Van BW, Vanholder R. A sad but forgotten truth: the story of slow-moving solutes in fast hemodialysis. Semin Dial. 2012;25(5):505–9.
6. Basile C, Libutti P, Di Turo AL, Casino FG, Vernaglione L, Tundo S, et al. Removal of uraemic retention solutes in standard bicarbonate haemodialysis and long-hour slow-flow bicarbonate haemodialysis. Nephrol Dial Transplant. 2011;26(4):1296–303.
7. Meijers B, Toussaint ND, Meyer T, Bammens B, Verbeke K, Vanrenterghem Y, et al. Reduction in protein-bound solutes unacceptable as marker of dialysis efficacy during alternate-night nocturnal hemodialysis. Am J Nephrol. 2011;34(3):226–32.
8. Ronco C, Ghezzi PM, Brendolan A, Crepaldi C, La GG. The haemodialysis system: basic mechanisms of water and solute transport in extracorporeal renal replacement therapies. Nephrol Dial Transplant. 1998;13 Suppl 6:3–9.
9. Davenport A. How can dialyzer designs improve solute clearances for hemodialysis patients? Hemodial Int. 2014;18 Suppl 1:S43–7.
10. Chapdelaine I, de Roij van Zuijdewijn CL, Mostovaya IM, Levesque R, Davenport A, Blankestijn PJ, et al. Optimization of the convection volume in online post-dilution haemodiafiltration: practical and technical issues. Clin Kidney J. 2015;8(2):191–8.
11. Clark WR, Gao D. Properties of membranes used for hemodialysis therapy. Semin Dial. 2002;15(3):191–5.
12. Daugirdas JT, Blake PG, Ing TS. Handbook of hemodialysis. 5th ed. Philadelphia: Wolters Kluwer; 2014.
13. Maduell F, Arias-Guillen M, Fontsere N, Ojeda R, Rico N, Vera M, et al. Elimination of large uremic toxins by a dialyzer specifically designed for high-volume convective therapies. Blood Purif. 2014;37(2):125–30.
14. Gubensek J, Buturovic-Ponikvar J, Ponikvar R, Cebular B. Hemodiafiltration and high-flux hemodialysis significantly reduce serum valproate levels inducing epileptic seizures: case report. Blood Purif. 2008;26(4):379–80.
15. Huang Z, Gao D, Letteri JJ, Clark WR. Blood-membrane interactions during dialysis. Semin Dial. 2009;22(6):623–8.
16. Shiraishi Y, Okajima M, Sai Y, Miyamoto K, Inaba H. Elimination of teicoplanin by adsorption to the filter membrane during haemodiafiltration: screening experiments for linezolid, teicoplanin and vancomycin followed by in vitro haemodiafiltration models for teicoplanin. Anaesth Intensive Care. 2012;40(3):442–9.
17. Bruni J, Wang LH, Marbury TC, Lee CS, Wilder BJ. Protein binding of valproic acid in uremic patients. Neurology. 1980;30(5):557–9.
18. Shinzato T, Miwa M, Nakai S, Takai I, Matsumoto Y, Morita H, et al. Alternate repetition of short fore- and backfiltrations reduces convective albumin loss. Kidney Int. 1996;50(2):432–5.
19. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Mazairac AH, Penne EL, et al. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. Kidney Int. 2014;86(2):423–32.
20. Swan SK, Bennett WM. Drug dosing guidelines in patients with renal failure. West J Med. 1992;156(6):633–8.
21. Patel K, Rayner CR, Giraudon M, Kamal MA, Morcos PN, Robson R, et al. Pharmacokinetics and safety of oseltamivir in patients with end-stage renal disease treated with automated peritoneal dialysis. Br J Clin Pharmacol. 2015;79(4):624–35.
22. Eschenauer GA, Lam SW. Supratherapeutic oseltamivir levels during continuous dialysis: an expected risk. Intensive Care Med. 2011;37(2):371.

23. Penne EL, van der Weerd NC, Blankestijn PJ, van den Dorpel MA, Grooteman MP, Nube MJ, et al. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. Clin J Am Soc Nephrol. 2010;5(1):80–6.
24. De Vriese AS, Caluwe R, Bailleul E, De BD, Borrey D, Van VB, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis. 2015. doi:10.1053/j.ajkd.2015.01.022 [Epub ahead of print].
25. Schmidt JJ, Lorenzen J, Chatzikyrkou C, Lichtinghagen R, Kielstein JT. Total collected dialysate lithium concentration after successful dialysis treatment in case of intoxication. BMC Pharmacol Toxicol. 2014;15:49.
26. Panichi V, Rosati A, Bigazzi R, Paoletti S, Mantuano E, Beati S, et al. Anaemia and resistance to erythropoiesis-stimulating agents as prognostic factors in haemodialysis patients: results from the RISCAVID study. Nephrol Dial Transplant. 2011;26(8):2641–8.
27. Vos FE, Schollum JB, Coulter CV, Doyle TC, Duffull SB, Walker RJ. Red blood cell survival in long-term dialysis patients. Am J Kidney Dis. 2011;58(4):591–8.
28. Gaweda AE, Goldsmith LJ, Brier ME, Aronoff GR. Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response. Clin J Am Soc Nephrol. 2010;5(4):576–81.
29. van der Weerd NC, den Hoedt CH, Blankestijn PJ, Bots ML, van den Dorpel MA, Levesque R, et al. Resistance to erythropoiesis stimulating agents in patients treated with online hemodiafiltration and ultrapure low-flux hemodialysis: results from a randomized controlled trial (CONTRAST). PLoS One. 2014;9(4):e94434.
30. Zhang K, Dong J, Cheng X, Bai W, Guo W, Wu L, et al. Association between vitamin C deficiency and dialysis modalities. Nephrology (Carlton). 2012;17(5):452–7.
31. Morena M, Cristol JP, Bosc JY, Tetta C, Forret G, Leger CL, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. Nephrol Dial Transplant. 2002;17(3):422–7.
32. Fehrman-Ekholm I, Lotsander A, Logan K, Dunge D, Odar-Cederlof I, Kallner A. Concentrations of vitamin C, vitamin B12 and folic acid in patients treated with hemodialysis and on-line hemodiafiltration or hemofiltration. Scand J Urol Nephrol. 2008;42(1):74–80.
33. Heinz J, Domrose U, Westphal S, Luley C, Neumann KH, Dierkes J. Washout of water-soluble vitamins and of homocysteine during haemodialysis: effect of high-flux and low-flux dialyser membranes. Nephrology (Carlton). 2008;13(5):384–9.
34. Sombolos KI, Fragia TK, Gionanlis LC, Veneti PE, Bamichas GI, Fragidis SK, et al. The anticoagulant activity of enoxaparin sodium during on-line hemodiafiltration and conventional hemodialysis. Hemodial Int. 2009;13(1):43–7.
35. de Roij van Zuijdewijn C, Nube MJ, Blankestijn PJ, ter Wee PM, van den Dorpel MA, Bots ML, et al. The prescribed dose of low molecular weight heparin increases after assigning patients to hemodiafiltration (HDF) treatment. J Am Soc Nephrol. 2014;25(abstract ed):292A.
36. Mahieu E, Claes K, Jacquemin M, Evenepoel P, De Op BK, Bogaert AM, et al. Anticoagulation with fondaparinux for hemodiafiltration in patients with heparin-induced thrombocytopenia: dose-finding study and safety evaluation. Artif Organs. 2013;37(5):482–7.
37. Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, Nube MJ, et al. Effect of increased convective clearance by on-line hemodiafiltration on all cause and cardiovascular mortality in chronic hemodialysis patients – the Dutch CONvective TRAnsport STudy (CONTRAST): rationale and design of a randomised controlled trial [ISRCTN38365125]. Curr Control Trials Cardiovasc Med. 2005;6(1):8.
38. Klingel R, Schaefer M, Schwarting A, Himmelsbach F, Altes U, Uhlenbusch-Korwer I, et al. Comparative analysis of procoagulatory activity of haemodialysis, haemofiltration and haemodiafiltration with a polysulfone membrane (APS) and with different modes of enoxaparin anticoagulation. Nephrol Dial Transplant. 2004;19(1):164–70.
39. Gritters-van den Oever M, Grooteman MP, Bartels PC, Blankestijn PJ, Bots ML, van den Dorpel MA, et al. Post-dilution haemodiafiltration and low-flux haemodialysis have dissimilar effects on platelets: a side study of CONTRAST. Nephrol Dial Transplant. 2009;24(11):3461–8.

40. Grau E, Siguenza F, Maduell F, Linares M, Olaso MA, Martinez R, et al. Low molecular weight heparin (CY-216) versus unfractionated heparin in chronic hemodialysis. Nephron. 1992;62(1):13–7.
41. Ljungberg B, Jacobson SH, Lins LE, Pejler G. Effective anticoagulation by a low molecular weight heparin (Fragmin) in hemodialysis with a highly permeable polysulfone membrane. Clin Nephrol. 1992;38(2):97–100.
42. Sridharan S, Berdeprado J, Sivalingam M, Farrington K. Dalteparin dosing in high-flux haemodialysis and haemodiafiltration. Nephron Clin Pract. 2012;122(1–2):53–7.
43. Sombolos KI, Fragia TK, Gionanlis LC, Veneti PE, Bamichas GI, Fragidis SK, et al. Use of fondaparinux as an anticoagulant during hemodialysis: a preliminary study. Int J Clin Pharmacol Ther. 2008;46(4):198–203.
44. Chang DN, Dager WE, Chin AI. Removal of dabigatran by hemodialysis. Am J Kidney Dis. 2013;61(3):487–9.
45. Buturovic-Ponikvar J, Gubensek J, Ponikvar R. Citrate anticoagulation for postdilutional online hemodiafiltration with calcium-containing dialysate and infusate: significant clotting in the venous bubble trap. Int J Artif Organs. 2008;31(4):323–8.
46. Tamme K, Oselin K, Kipper K, Low K, Standing JF, Metsvaht T, et al. Pharmacokinetics of doripenem during high volume hemodiafiltration in patients with septic shock. J Clin Pharmacol. 2015;55(4):438–46.
47. Hafner V, Czock D, Burhenne J, Riedel KD, Bommer J, Mikus G, et al. Pharmacokinetics of sulfobutylether-beta-cyclodextrin and voriconazole in patients with end-stage renal failure during treatment with two hemodialysis systems and hemodiafiltration. Antimicrob Agents Chemother. 2010;54(6):2596–602.
48. Molto J, Sanz-Moreno J, Valle M, Cedeno S, Bonal J, Bouarich H, et al. Minimal removal of raltegravir by hemodialysis in HIV-infected patients with end-stage renal disease. Antimicrob Agents Chemother. 2010;54(7):3047–8.
49. Oh KH, Kim C, Lee H, Lee H, Jung JY, Kim NJ, et al. Pharmacokinetics of intravenous piperacillin administration in patients undergoing on-line hemodiafiltration. Antimicrob Agents Chemother. 2009;53(8):3266–8.
50. Basile C, Di MA, Curino E, Scatizzi A. Pharmacokinetics of netilmicin in hypertonic hemodiafiltration and standard hemodialysis. Clin Nephrol. 1985;24(6):305–9.
51. Sombolos K, Fytili C, Fragidis S, Victoria H, Bamichas GI, Natse TA. On-line hemodiafiltration reduces serum gentamicin levels much more efficiently than conventional hemodialysis. Dial Transplant. 2010;39(10):453–4.
52. Thalhammer F, Rosenkranz AR, Burgmann H, Graninger W, Hollenstein U, Schenk P, et al. Single-dose pharmacokinetics of teicoplanin during hemodialysis therapy using high-flux polysulfone membranes. Wien Klin Wochenschr. 1997;109(10):362–5.
53. Ariano RE, Fine A, Sitar DS, Rexrode S, Zelenitsky SA. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. Am J Kidney Dis. 2005;46(4):681–7.
54. Sombolos KI, Fragidis SK, Bamichas GI, Hatsiou VN, Rizos AK, Natse TA, et al. Subtherapeutic serum vancomycin concentrations during on-line hemodiafiltration. ASAIO J. 2011;57(6):507–10.
55. Konishi K, Suzuki H, Saruta T, Hayashi M, Deguchi N, Tazaki H, et al. Removal of imipenem and cilastatin by hemodialysis in patients with end-stage renal failure. Antimicrob Agents Chemother. 1991;35(8):1616–20.
56. Marchand S, Frat JP, Petitpas F, Lemaitre F, Gobin P, Robert R, et al. Removal of colistin during intermittent haemodialysis in two critically ill patients. J Antimicrob Chemother. 2010;65(8):1836–7.
57. Izzedine H, Launay-Vacher V, Peytavin G, Valantin MA, Deray G. Atazanavir: a novel inhibitor of HIV-protease in haemodialysis. Nephrol Dial Transplant. 2005;20(4):852–3.
58. Treitel M, Marbury T, Preston RA, Triantafyllou I, Feely W, O'Mara E, et al. Single-dose pharmacokinetics of boceprevir in subjects with impaired hepatic or renal function. Clin Pharmacokinet. 2012;51(9):619–28.
59. Ashley C, Currie A. The renal drug handbook. 3rd ed. London: Radcliffe Publishing Ltd; 2008.

Part VI
Summary and Conclusions

Chapter 25
Summary and Current Status of Hemodiafiltration

Menso J. Nubé, Muriel P.C. Grooteman, and Peter J. Blankestijn

Abstract In this last chapter, the contents of the Hemodiafiltration: Theory, Technology and Clinical Practice are summarized according to the various subjects discussed, instead of reviewing all 25 chapters separately. First, a short overview is given of the various hemodiafiltration (HDF) modalities, including some of their pros and cons. As most clinical studies were performed in the online postdilution mode, most attention is paid to this type of HDF. Most important, of course, are the results of online HDF on clinical outcome parameters and various biomarkers. After that, attention is paid to the potential mechanisms behind the beneficial effects of high volume HDF on outcome. After a short discussion on topics which should be further exploited, some disadvantages and practical issues when implementing a HDF program are reviewed. This chapter comes to an end with a vision on the future, including the responsibility of institutions and the nephrology community.

Keywords Hemodiafiltration • Clinical outcome • Biomarkers • Mechanisms • Disadvantages • Future aspects

Introduction

In the past decades, online hemodiafiltration (HDF) has been developed towards a safe and effective treatment that is widely applied nowadays. In this last chapter we give an overview of the contents of this book, and reflect on the current place and the future of hemodiafiltration. For references please have a look at the respective chapters.

M.J. Nubé, MD, PhD (✉) • M.P.C. Grooteman, MD, PhD
Department of Nephrology, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081 HV, The Netherlands
e-mail: mensonube@gmail.com

P.J. Blankestijn, MD
Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_25

Modes of Hemodiafiltration

As described in Chap. 2, in HDF the diffusive capacity of low-flux HD and the convective transport of hemofiltration are combined. Strictly speaking, high-flux HD is a type of HDF, as the trans-membrane-pressure (TMP) gradient in the proximal part of the dialyzer promotes the transfer of water and larger solutes from the blood to the dialysate. As the hydraulic pressure on the blood side drops progressively along the fibers while oncotic pressure increases concomitantly, TMP reverses its direction and water moves from the dialysate to the blood. This mechanism, called 'internal filtration', is the underlying principle of convection in high-flux HD and has been estimated 10–12 L/treatment.

Post-dilution online infusion is todays most widespread infusion mode in hemodiafiltration and the most efficient in removing middle molecules, such as β2-microglobulin (β2M: 11.8 kD). Sterile substitution fluid is produced online from the dialysate and infused post-filter to replace the excess ultrafiltration (UF). Up to 5–7 L UF per hour can obtained by applying appropriate flux-pressure regimens.

Pre-dilution hemodiafiltration offers more favorable rheological and hydraulic conditions than the post-dilution mode, by better preserving the permeability of the membrane, as the infusion site of the replacement fluid at the dialyzer inlet prevents excessive hemoconcentration and clotting in the dialyzer. This advantage may be offset by the diluting effect on plasma solute concentrations available for diffusion and convection, with consequent reduction of the cumulative solute mass transfer. Clinical application of pre-dilution HDF is limited by these drawbacks and may be indicated in patients with a high hematocrit and in patients with a contra-indication for intravenous administration of anticoagulants.

Several other techniques are applied, such as acetate free biofiltration, mixed hemodiafiltration, and mid-dilution hemodiafiltration. The latter two were developed with the aim to overcome the limits and risks of pre- and post dilution HDF, while coupling their advantages. Little clinical data on these techniques are available as of yet.

Results of Hemodiafiltration on Clinical Outcome

Influence of HDF on Mortality

As listed in Chap. 16, many reports have been published on the clinical effects of HDF, which, however, vary considerably in the techniques compared, reference arms, achieved convection volume in HDF patients, study design, end points and patient numbers. As these studies are hard to interpret and three recent RCTs (CONTRAST, the Turkish HDF Study and ESHOL), all comparing online post-dilution HDF with HD, are the only large studies with mortality as a primary end point, the results on all-cause and cardiovascular mortality as discussed below are mainly derived from these studies.

While neither CONTRAST nor the THDFS showed a difference in clinical outcome between treatment arms, ESHOL did find a favorable effect of HDF on overall survival. Both ESHOL and THDFS showed a lower, albeit non-significant, cardiovascular mortality risk in HDF patients. *Post-hoc* analyses of all three RCTs showed a positive relationship between the magnitude of the convection volume and clinical outcome, as suggested before in observational studies.

Notably, in the last 2 years, four meta-analyses on convective therapies have been published, pooling the aggregated results of separate investigations, which, however, showed discrepant conclusions. The only meta-analysis which included only HDF clearly showed an all-cause and cardiovascular survival advantage of HDF over HD (HR 0.84; 95 % CI 0.73–0.96 and 0.73; 95 % CI 0.57–0.92, resp). Of note, after removing low volume/*offline* HDF (including AFB) from one of the other meta-analyses, a comparable conclusion was reached (HR for mortality HDF 0.82; 95 % CI 0.72–0.93). Similar results were obtained in a recent meta-analysis on individual patient data (IPD). The largest survival benefit was obtained in the group of patients receiving the highest convection volume (>23 L/1.73 m^2/session). In these subjects, the adjusted HR for all-cause mortality was 0.78; 95 % CI 0.62–0.98, and for cardiovascular mortality 0.69; 95 % CI 0.47–1.00.

Besides a high risk of cardiovascular death, ESKD patients also have an elevated risk of non-cardiovascular mortality. Since the excess mortality in ESKD follows a 'normal' distribution, it is interesting to know whether the reduced mortality in HDF patients is mainly due to a decline in cardiovascular events or also to a lower incidence of other causes. Actually, as shown in the IPD meta-analysis, no evidence whatsoever was obtained that infection-related mortality or other causes of death, such as withdrawal from dialysis or malignancies, were different between HDF and control patients. Hence, it seems justified to conclude that the reduction in all-cause mortality in HDF is mainly caused by a decrease in fatal cardiovascular events.

Influence of HDF on Other Clinical Conditions

As described in Chap. 17, intradialytic hypotension (IDH) is an important complication of dialysis treatment, which has been related to bowel hypoperfusion, brain white matter ischaemia, cardiac stunning and mortality. In two large RCTs, blood pressure stability during HDF was superior to HD, but not in a third. When cool dialysate (CD-HD) was used in both groups, changes in blood pressure (BP), blood volume, cardiac output and microcirculation, did not differ. Hence intradialytic hemodynamic stability appears better preserved during HDF than during conventional HD, but analogous to CD-HD. The contribution of this mechanism to the survival advantage of high volume HDF is more extensively discussed in Chap. 19. With respect to pre- and postdialysis BP, mean arterial pressure and pulse pressure, differences were not found. Altogether, it appears that HDF improves IDH, without marked beneficial hemodynamic changes in the interdialytic interval.

Influence of HDF on Various Biomarkers

As outlined in Chap. 13, ESKD patients suffer from a micro-inflammatory state which has been partly related to the bio-incompatibility of HD treatment itself and partly to the accumulation of uremic toxins. Since especially MMW compounds have been implicated in this process, a switch from HD to HDF may improve this condition. On the other hand, administration of large amounts of substitution fluid may worsen inflammation by the infusion of bacterial-derived and chemical contaminants. Therefore it is reassuring to note that HDF is at least as safe as HD and possibly better. Cross-over trials described both lower and similar C-reactive protein (CRP) levels, a lower number of CD14+CD16+ cells and a lower production of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) in HDF patients as compared to HD. A secondary analysis of CONTRAST showed stable IL-6 and CRP levels over time in HDF and an increase in HD patients. Since CRP levels over time did not differ in ESHOL and THDFS between the HD and HDF groups, it appears that HDF is a safe treatment with, if anything, a beneficial effect on inflammation.

The effect of convective techniques on renal anemia has been thoroughly investigated, as ESA resistance might be induced by the (chapter 12) retention of MMW solutes. Although observational studies suggested a beneficial effect of HDF, this could not be confirmed in randomized trials. Only very few studies on the effect of convective therapies on nutritional state have been performed (chapter 18), precluding firm results. Finally, CKD-MBD (chapter 11) might be positively influenced by treatment with HDF, as fibroblast growth factor 23 (FGF23) removal is higher during convective treatments, and phosphate levels are lower. The clinical effects of these changes remain to be established.

Why Is High Volume HDF Associated with Improved Survival?

As extensively discussed in Chap. 16, HDF, especially when applied with high convection volumes, is strongly related to an improved cardiovascular survival. So, what are the underlying mechanisms? As published in individual RCTs and by meta-analysis, HDF may improve intradialytic hemodynamic stability. Moreover, echocardiographic analysis indicates that the deterioration of the left ventricle over time as observed in HD patients was mitigated or even absent in the HDF group. Convincing arguments are not available that HDF reduces cardiovascular mortality by improvements in traditional or non-traditional risk factors. With respect to solute removal, neither Kt/V_{urea}, β2M or any other single uremic retention product has been specifically related to clinical outcome in HDF. Whether high doses of heparin or better correction of acidosis adds to the reduced mortality in HDF is a matter for future research. For further reading see Chap. 19.

Areas in HDF That Should Be Further Exploited

As mentioned in Chap. 20, HDF was already performed in children in the early 1980s. Advances in technology with dialysis machines that allow controlled UF and smaller dialysis filters enabled the use of online HDF as a safe therapy in children. Using in-centre intensive HDF for 5 days a week, children were free of symptoms and post-dialysis recovery time, with few or no medication requirements, a normal diet and optimized volume control on a free fluid intake. These features allowed catch-up growth with normal height. Currently, an international non-randomised clinical trial is in progress to compare the effects of HDF versus conventional HD on growth and cardiovascular markers.

Observational data indicate that frequent dialysis schemes reduce fluctuations in metabolic and volume parameters, if compared with thrice-weekly schedules. A recent review suggested that these schemes (daily, nocturnal or every-other-day) significantly improve blood pressure control, CKD-MBD and quality of life. As mentioned in Chap. 21, limited data are available on extended HDF schedules, such as short daily online HDF and nocturnal, every-other-day online HDF. One year after the switch from standard HDF to daily online HDF, there was an increase in body weight, better blood pressure control and a marked regression of left ventricular hypertrophy. Local infections, thrombosis or bleeding of the vascular access were not observed. Likewise, conversion from 4 to 5 h thrice weekly standard HDF to nocturnal online-HDF showed excellent clinical tolerance and patient acceptance, adequate social and occupational rehabilitation, better dialysis adequacy, marked improvement in nutritional status, regression of LVH, good phosphate and hypertension control with less medication. Hence, it appears that intensified HDF, either applied daily for 2–3 h or every-other-day at night for 7–8 h, is associated with improvements in clinical and social-occupational rehabilitation. These attractive results await confirmation in a prospective trial.

Disadvantages and Side-Effects of Hemodiafiltration

Apart from its beneficial effects on survival, treatment with HDF also has been associated with undesirable reactions, such as complement activation and platelet activation, as outlined in Chaps. 15 and 22. Due to the high TMP and hemoconcentration within the dialyzer, these effects are pronounced in online postdilution HDF, as indicated by the degree of platelet activation and need for heparin. Moreover, during HDF, unwanted loss of nutrients may occur, such as vitamin C and albumin. Furthermore, due to the high convection volume, kinetics and dynamics of frequently prescribed oral and intravenous medication during HDF may be different from HD, as described in Chap. 24. Finally, it is conceivable that an enhanced convective transport of MMW uremic toxins in HDF may be accompanied by an undesirable removal of useful metabolic and hormonal substances. However, since high

volume HDF is associated with a better clinical outcome than HD, the balance between desired removal and unwanted losses is probably most favorable during HDF treatment.

Practical Aspects

Just performing post-dilution online HDF does not automatically result in high convection volumes. As described in Chap. 23, the magnitude of the convection volume appears mainly determined by treatment-related factors and only to a limited extent by patient characteristics. From a retrospective analysis in CONTRAST patients, it appeared that blood flow and treatment time are the main determinants of the convection volume. Interestingly, while the convection volume varied roughly between 15 and 23 L/session, in some facilities, *all* patients were treated with exactly the same blood flow rate or treatment time, suggesting that center policy rather than patient characteristics is an important determinant of the magnitude of the convection volume in every day clinical practice.

Especially an increase in treatment time and blood flow rate (with matching needle size) will improve convection volumes. Although in general, lower blood flow rates are attained with a central venous catheter as compared to an AV fistula or graft, a CVC is not a contra-indication for high volume HDF. As for the choice of the dialyzer, the highest convection volumes are obtained with a large membrane surface area (>2 m^2), a high UF coefficient (>55 mL/mmHg/h), a wide capillary lumen diameter (>200 μm) and intermediate capillary length; more research on this topic is needed. For more details on dialyzers see Chap. 4. Finally, it should be mentioned that adequate anticoagulation is mandatory in high volume HDF, as the high TMP needed for high UF volumes and the resulting hemoconcentration may induce premature filter clotting. In clinical practice, the dose of the prescribed anticoagulant was 10–25 % higher in HDF than in HD patients. Finally, training of the team, avoidance of recirculation, constant awareness and re-evaluation of the treatment and treatment goals at a regular basis are of utmost importance. Key requirements for performing high volume postdilution online HDF are mentioned in Table 25.1.

Implementation of HDF and Vision on the Future

The percentage of ESKD patients that is treated with HDF shows considerable variability worldwide, being 15–20 % in Europe, 8 % in Japan and virtually nil in the USA. Accepting the fact that mortality is reduced by approximately 30 % in high volume HDF, what are the reasons not to implement HDF as a first choice treatment? First, practitioners may not yet be convinced about the superiority of high volume HDF, because RCTs showed conflicting results and the dose-response effect was obtained from *post hoc* analyses. Second, achievement of high volume HDF

Table 25.1 Key requirements for performing high volume postdilution HDF

Center level
Presence of modern dialysis machines, water treatment and delivery system
Technical staff able to deliver online HDF matching quality reference standards
Dialysis staff adequately trained on and aware of specific features of online HDF, also including the fact that a certain minimum dose is necessary to obtain full benefit
Patient level
No specific subgroup of ESKD patients has been identified to benefit more than others. So, HDF may be choice of treatment for a wide range of ESKD patients
Vascular access should be able to deliver a blood flow 350–400 mL/min in the extracoporeal circuit. In order to limit the risk of (frequent) machine alarms, it seems advisable that an arteriovenous fitula or graft should have a flow of at least 600 mL/min
Dialysis over a central venous catheter is not a contra-indication to perform high volume HDF beforehand

necessitates extra training, attention and efforts from the technical and medical staff, as the high TMP and high filtration fraction may lead to bothersome alarms and sometimes interruption of the treatment. Third, while online production of fluids (so-called "cold sterilization") is officially accepted by the European Medicines Agency (EMA), this is not the case for the US Federal Drug Agency (FDA).

How should we proceed? Most importantly, the dialysis industries should make reliable water treatment systems and dialysis machines, able to deliver high dose HDF consistently, and without interruptions and frequent machine alarms. For the nephrologic community it may be time for a paradigm shift, since the dose of dialysis treatment should be based on the magnitude of the convection volume rather than on (changes in) biochemical variables. The dialysis staff should be trained and motivated to operate the dialysis machines in such a way that the predefined amount of convection volume will be achieved in everyday clinical practice. Notably, high volume HDF can be performed in the same organizational and logistical infrastructure as is currently available in most centers in the Western world. Since online HDF has the potential of being one of the few real breakthroughs in nephrology over decades, an "end of discussion" trial, comparing high volume HDF with HD, should be done in the near future, taking not only 'hard endpoints' into account, but also patient's well being. Lastly, to further optimize HDF additional studies should be designed to clarify the potential mechanisms behind its beneficial effects.

Responsibility of Institutions, Insurance Companies and the Nephrologic Community

Although the "end of discussion" trial has not yet started, the available evidence indicates that HDF has a beneficial effect on survival. Moreover, modern HDF is at least as safe and probably also cost-effective. Therefore, first, the FDA should

reconsider their moratorium on the cold sterilization process, as thousands of American ESKD patients are now restrained from a mode of dialysis therapy that may prolong their lives without loss of well being. Second, health insurance companies should promote and accept high volume HDF as first choice treatment, because it most likely offers the best therapy within the presently accepted thrice-weekly treatment schedule. Lastly, the nephrologic community should implement high volume HDF in every day clinical practice, since we have the obligation to offer the highest level of care to our patients.

Index

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1