

Why is on-line haemodiafiltration necessary as a renal replacement therapy option in chronic kidney disease patients?

Bernard Canaud^{1,2}

¹ Nephrology, Dialysis and Intensive Care.

Lapeyronie University Hospital. Montpellier, France

² Renal Research and Training Institute. Montpellier, France

Received for publication: 01/04/2007

Accepted in revised form: 15/05/2007

■ INTRODUCTION

It has been clearly shown over the last three decades that conventional haemodialysis (HD) is a very efficacious form of treatment which has increased the lifespan of more than one and half million chronic kidney disease stage 5 (CKD-5) patients worldwide. In contrast to this success story, the high morbidity and mortality rate still persisting in dialysis patients is, however, the upcoming renal replacement therapy (RRT) challenge. Further, it is frustrating for clinicians to note that despite major technical advances (among which are high-flux membranes, bicarbonate buffered dialysis fluid, ultrafiltration controlled machines, biocompatible material) and leading therapeutic achievements (correction of anaemia by erythropoietic stimulating agents (ESAs), correction of hyperlipidemia and so on) in RRT, there have been no significant progress in patient outcomes.

The increasing prevalence of dialysis-related pathology, including β_2 M-amyloidosis, accelerated atherosclerosis, left ventricular hypertrophy, ageing and malnutrition in long term treated patients, are other factors contributing to the partial failure of conventional RRT. While the precise causes of this dialysis-related pathology are not fully known, it can be speculated that several mechanisms contribute to the outcome.

To some extent, pathophysiologic mechanisms combine four main factors: limited clearance of mid-

dle solutes leading to the accumulation of middle and large uraemic toxins; poor biocompatibility of the dialysis system responsible for the periodic activation of cells and protein systems resulting in a microinflammation state; unphysiologic profile of intermittent treatment leading to alternate peaks and troughs and unfavourable correction of the *milieu interieur* composition, leaving metabolic disturbances such as permanent oxidative and carbonyl stress condition.

■ WHAT IS DIFFERENT ABOUT ON-LINE HAEMODIAFILTRATION?

Conventional diffusive-based dialysis modalities, including high-flux haemodialysis, are limited in their clearance of medium sized uraemic toxins. Convective methods which mimic the glomeruli filtration of native kidneys are required to enlarge the molecular weight spectrum of solutes removed during the dialysis session. On-line haemodiafiltration (ol-HDF) provides several advantages here. It combines diffusive and enhanced convective clearances, making it the most efficient modality for clearing small and medium uraemic toxins¹⁻³. Additionally, by using ultrapure dialysis fluid and high-flux synthetic membranes, it offers the most biocompatible dialysis system⁴⁻⁵. Moreover, as it

provides a virtually unlimited amount of sterile dialysis fluid by cold sterilisation filtration, it is an economical method for achieving high efficiency HDF (high fluid volume exchange) therapy with all substitution mode⁶⁻⁷ and as it maintains dialysis machine hardware options (fluid balancing system, thermal balance, blood volume monitoring, etc.), it retains the best technical options for optimising treatment efficacy and tolerance.

■ WHAT ARE THE TECHNICAL PREREQUISITES FOR STARTING OL-HDF?

ol-HDF methods require specific technical options and careful clinical monitoring to ensure safety and optimal performances. The summary below shows that this is not a big issue and can be easily provided in most dialysis facilities.

Patients should be equipped with a vascular access regularly providing an extracorporeal blood flow of 400ml/min. A high-flux dialyser is required to perform ol-HDF. Several dialysers made of synthetic polymers are available on the market. High flux dialysers share in common a dialysis membrane with high hydraulic permeability ($K_{UF} \geq 50$ ml/h/mmHg), high solute permeability ($K_{O_A \text{ urea}} > 600$ and $\beta_{2\text{-microglobulin}} > 60$ ml/min) and large surface of exchange (1.50 to 2.10 m²).

Certified ol-HDF machines (blood monitoring and dialysate proportioning system) especially designed to safely achieve the dialysis session and to monitor treatment are needed. Bicarbonate-based dialysate solution and ultrafiltration controller have been generalised in dialysis machines, making dialysis sessions much smoother.

Ultrapure dialysate is a standard for ol-HDF machines. This is currently achieved by feeding dialysis machines with ultrapure water. The production of sterile and non-pyrogenic dialysis and substitution fluids is warranted by on-line cold sterilisation of the dialysate based on two sterilising ultrafilters interposed on the inlet dialysate line⁸. Sterility and microbial safety of the HDF machines is currently achieved by combining frequent heat and chemical disinfection procedures.

■ WHAT ARE THE CLINICAL BENEFICIAL EFFECTS OF OL-HDF?

Several reports have evidenced that the regular use of high efficiency HDF has beneficial effects on long-term dialysis patients.

Improvement of dialysis session tolerance is repeatedly reported with high efficiency HDF modalities⁹⁻¹⁰. Incidence of hypotensive episodes is reduced with HDF methods despite the significant weight loss¹¹. This is particularly important in hypotensive-prone and cardiac patients¹². This effect has been attributed to a positive vasomodulation effect involving several factors including a negative thermal balance, a high sodium concentration of the substitution fluid, the removal of vasodilating mediators and the absence of dialysate-derived contaminants^{13,14}. Post-dialysis fatigue is reduced with ol-HDF. This is particularly useful in elderly, diabetic, and other high risk patients¹⁵.

A better control of arterial pressure has been reported with high efficiency convective therapies¹¹. This beneficial effect is mainly due to the intradialytic haemodynamic stability that allows dry weight to be reached and to restore the sodium fluid balance more appropriately¹⁶. Length of sessions and compliance with a low sodium diet are also required to facilitate achievement of this primary objective. This positive effect is associated with a better anaemia correction and an adequate blood pressure control, suggesting that the effect may be linked to specific properties of ol-HDF^{17,18}.

High efficiency ol-HDF based on the regular use of ultrapure dialysate reduces the microinflammation of the HD patient. Based on sensitive markers of the acute phase reaction (CRP, IL1, IL6, IL1- and IL6-RA, albumin), several prospective studies have shown that the behaviour of these markers remains stable in the normal range over time in ol-HDF treated patients¹⁹. Preventing inflammation is a crucial target in order to reduce the incidence of dialysis-related complications in long-term dialysis patients²⁰.

Caloric and/or protein malnutrition is commonly observed in about one third of dialysis patients. Several recent studies have shown that the use of high flux membranes has a positive impact on the nutritional state as compared to low flux membranes²¹. Serum albumin as well as dietary protein intake tends to

increase when patients are treated with high flux membranes²². Indeed, one must recognise that this positive effect might stem from the combination of using high flux membranes with ultrapure dialysate and possibly by eliminating anorexia, and removing uraemic toxins via convective flux^{23,24}.

The regular use of high flux membranes with enhanced convective clearances has been shown to improve lipid profile^{25,26} and to reduce oxidative stress and AGEs in CKD-5 patients²⁷. While not fully understood, this beneficial effect may be partly due to the improved biocompatibility of the dialysis system associated with the combined use of synthetic membrane and ultrapure dialysate^{28,29}.

Neuropathy is a rare complication of RRT that is considered as a late marker of inadequate dialysis. It has been reported that intensification of treatment with high-efficiency convective methods can correct this neuropathy^{30,31}.

Renal anaemia, commonly observed in HD patients, requires EPO use in 80 to 100% of patients. Although controversial, it has been reported that high efficiency convective therapies were able to improve anaemia and to reduce EPO needs^{32,33}. This positive effect is particularly well illustrated when patients are switched from low-flux to high-efficiency HDF modalities or to HD using high-flux protein-leaking membranes. These observations suggest that high flux convective methods might remove protein-bound erythropoietic inhibitor substances³⁴.

Growth retardation is a major concern in CKD-5 children. This is a source of psychological difficulties during childhood. Conventional haemodialysis alone has not been able to reverse this development retardation. A recent study based on a daily ol-HDF schedule has been proved to correct growth in children with chronic kidney disease³⁵. This beneficial effect is achieved by combining a more efficacious treatment with an enhanced dietary and caloric intake and correction of *milieu interieur* disturbances (acidosis, calcium and phosphate control)³⁶. The combined use of growth hormone (GH), erythropoietic stimulating agents (ESA) and ol-HDF provides the opportunity to normalise growth rate in children with CKD^{37,38}.

Beta₂-microglobulin amyloidosis is a major disabling complication of long-term HD treated patients. Using carpal tunnel syndrome as crude and first manifesta-

tion of beta₂-microglobulin amyloidosis, it is commonly accepted that the incidence reaches 50% at 10 years and 100% at 20 years with conventional low-flux HD treatment. Several retrospective database studies indicate that regular use of high flux membranes in HD³⁹ and enhanced convective therapies such as ol-HDF may reduce its incidence by 50%^{40,41}. An interpretation of this beneficial effect is not easy due to the presence of several confounding factors. Enhanced removal of medium sized uraemic toxins and reduced inflammation appear, however, to be the most prominent protective factors⁴².

Morbidity and mortality are the most robust endpoints used to compare the efficacy of renal replacement therapy modalities. Here, the negative results of the HEMO-study reported recently with patients receiving either high dialysis dose or high flux membrane were relatively disappointing⁴³. It is, however, interesting to mention that the use of high flux membrane was associated with a reduced incidence of cardiovascular events. A recent reappraisal analysis of the HEMO-study has shown that high predialysis B₂M concentrations were strong and independent predictors of mortality in HD patients. This observation suggests that enhanced removal of medium sized uraemic toxins is beneficial for CKD patients. The European part of the DOPPS study has shown that high-efficiency HDF-treated patients had a better survival than regular HD treated patients in terms of age, sex, dialysis dose, comorbid conditions and country specificities⁴⁴. The relative risk of death was reduced by 35 percent in HDF treated patients compared to low flux HD patients. Independent investigators recently confirmed this positive finding when analysing a large European database (Euclid). The relative risk of death was reduced in this study by 36 percent in HDF treated patients⁴⁵. It has also been observed in a retrospective US study that high efficiency HDF based on two filters in series was able to reduce mortality in HDF by 65%⁴⁶.

■ WHAT IS NEEDED NOW?

High-efficiency ol-HDF currently offers the most effective and biocompatible renal replacement therapy modality in CKD-5 patients. Ol-HDF has several properties. It enlarges the spectrum of medium sized

uraemic toxins cleared, improves the haemocompatibility profile of the dialysis system and reduces the mortality risk in long-term haemodialysis patients.

Using either a daily treatment schedule or long slow nocturnal HDF programme, the weekly cumulative body solute clearance is enhanced by 80% while the *milieu interieur* composition change is reduced. Extended treatment time and/or frequency with the ol-HDF therapy provides an optimal, safe and effective form of renal replacement therapy for CKD patients⁴⁷.

What still remains to confirm the superiority of ol-HDF? Prospective randomised clinical trials comparing high flux HD to high efficiency ol-HDF are still lacking but this scientific evidence will certainly be provided by the prospective randomised trials currently ongoing in Europe^{48,49}.

Conflict of interest statement. None declared.

References

- Maduell F, Navarro V, Cruz MC, Torregrosa E, Garcia D, Simon V, Ferrero JA. Osteocalcin and myoglobin removal in on-line hemodiafiltration versus low- and high-flux hemodialysis. *Am J Kidney Dis* 2002;40:582-9.
- Lornoy W, De Meester J, Becaus I, Billioux JM, Van Malderen PA, Van Potelberge M. Impact of convective flow on phosphorus removal in maintenance hemodialysis patients. *J Ren Nutr* 2006;16:47-53.
- Krieter DH, Lemke HD, Canaud B, Wanner C. Beta(2)-microglobulin removal by extracorporeal renal replacement therapies. *Biochim Biophys Acta* 2005;1753:146-53.
- Canaud B, Wizemann V, Pizzarelli F, Greenwood R, Schultze G, Weber C, Falkenhagen D. Cellular interleukin-1 receptor antagonist production in patients receiving on-line haemodiafiltration therapy. *Nephrol Dial Transplant* 2001;16:2181-7.
- Malyszko JS, Malyszko J, Hryszko T, Kozminski P, Pawlak K, Mysliwiec M. Markers of endothelial damage in patients on hemodialysis and hemodiafiltration. *J Nephrol* 2006;19:150-4.
- Weber C, Groetsch W, Schlottter S, Mitteregger R, Falkenhagen D. Novel online infusate-assisted dialysis system performs microbiologically safely. *Artif Organs* 2000;24:323-8.
- Canaud B, Levesque R, Krieter D, Desmeules S, Chalabi L, Moragues H, Morena M, Cristol JP. On-line hemodiafiltration as routine treatment of end-stage renal failure: why pre- or mixed dilution mode is necessary in on-line hemodiafiltration today? *Blood Purif* 2004;22 Suppl 2:40-8.
- Canaud B, Bosc JY, Leray H, Morena M, Stec F. Microbiologic purity of dialysate: rationale and technical aspects. *Blood Purif* 2000;18:200-13.
- Wizemann V, Kramer W, Knopp G, Rawer P, Mueller K, Schutterle G. Ultra-short hemodiafiltration: efficiency and hemodynamic tolerance. *Clin Nephrol* 1983;19:24-30.
- Movilli E, Camerini C, Zein H, D'Avolio G, Sandrini M, Strada A, Maiorca R. A prospective comparison of bicarbonate dialysis, hemodiafiltration, and acetate-free biofiltration in the elderly. *Am J Kidney Dis* 1996;27:541-7.
- Petrus D, Fortunato A, Soffiati G, Brendolan A, Bonello M, Crepaldi C, Ratanarat R, Campolo G, Amato M, Ronco C. Sequential convective therapies (SCT): a prospective study on feasibility, safety, adequacy and tolerance of on-line hemofiltration and hemodiafiltration in sequence. *Int J Artif Organs* 2005;28:482-8.
- Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G, Orlan-dini G. Effects of different membranes and dialysis technologies on patient tolerance and nutritional parameters. The Italian Cooperative Dialy-sis Study Group. *Kidney Int* 1996;50:1293-302.
- van Kuijk WH, Buurman WA, Gerlag PG, Leunissen KM. Vascular reactivity during combined ultrafiltration-hemodialysis: influence of dialysate-derived contaminants. *J Am Soc Nephrol* 1996;7:2664-9.
- 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.
- Mion M, Kerr PG, Argiles A, Canaud B, Flavier JL, Mion CM. Haemodiafil-tration in high-cardiovascular-risk patients. *Nephrol Dial Transplant* 1992;7:453-4.
- Takenaka T, Tsuchiya Y, Suzuki H. High-performance hemodiafiltration and blood pressure stability. *Nephron* 1997;75:30-5.
- Drueke TB, Eckardt KU, Frei U, et al.: Does early anemia correction pre-vent complications of chronic renal failure? *Clin Nephrol* 1999; 51:1
- Horl MP, Horl WH: Hemodialysis-associated hypertension: pathophysiology and therapy. *Am J Kidney Dis* 2002;39:227
- Vaslaki L, Weber C, Mitteregger R, Falkenhagen D. Cytokine induction in patients undergoing regular online hemodiafiltration treatment. *Artif Organs* 2000;24:514-8.
- Deppisch RM, Beck W, Goehl H, et al.: Complement components as ure-mic toxins and their potential role as mediators of microinflammation. *Kid-ney Int Suppl* 78:S271, 2001
- Lindsay RM, Spanner E, Heidenheim AP, et al.: A multicenter study of short hour dialysis using AN69S. Preliminary results. *ASAIO Trans* 37:M465, 1991
- Savica V, Ciolino F, Monardo P, Mallamace A, Savica R, Santoro D, Belling-hieri G. Nutritional status in hemodialysis patients: options for on-line con-vective treatment. *J Ren Nutr* 2006;16:237-40.
- Schiff H, Lang SM, Stratakis D, et al.: Effects of ultrapure dialysis fluid on nutritional status and inflammatory parameters. *Nephrol Dial Transplant* 16:1863, 2001
- Wiesholzer M, Harm F, Hauser AC, Pribasni 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;94:431-5.
- House AA, Wells GA, Donnelly JG, Nadler SP, Hebert PC. Randomized trial of high-flux vs low-flux haemodialysis: effects on homocysteine and lipids. *Nephrol Dial Transplant* 2000;15:1029-34.
- Blanketstijn PJ, Vos PF, Rabelink TJ, et al.: High-flux dialysis membranes improve lipid profile in chronic hemodialysis patients. *J Am Soc Nephrol* 5:1703,1995
- Chun-Liang L, Chiu-Ching H, Chun-Chen Y et al.: Reduction of advanced glycation end products levels by on-line hemodiafiltration in long-term hemo-dialysis patients. *Am J Kidney Dis* 42:524, 2003
- Ward RA, McLeish KR: Oxidant stress in hemodialysis patients: what are the determining factors? *Artif Organs* 27:230, 2003
- Wanner C, Bahner U, Mattern R, Lang D, Passlick-Deetjen J. Effect of dialy-sis flux and membrane material on dyslipidaemia and inflammation in hae-modialysis patients. *Nephrol Dial Transplant* 2004;19:2570-5.

- 30Malberti F, Surian M, Farina M, Vitelli E, Mandolfo S, Guri L, De Petri GC, Castellani A. Effect of hemodialysis and hemodiafiltration on uremic neuropathy. *Blood Purif* 1991;9(5-6):285-95.
- 31Tattersall JE, Cramp M, Shannon M, *et al.*: Rapid high-flux dialysis can cure uraemic peripheral neuropathy. *Nephrol Dial Transplant* 7:539, 1992
- 32Bonforte 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; 20:357-63.
- 33Vaslaki 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; 24:163-73.
- 34Yamada S, Kataoka H, Kobayashi H, Ono T, Minakuchi J, Kawano Y. Identification of an erythropoietic inhibitor from the dialysate collected in the hemodialysis with PMMA membrane (BK-F). *Contrib Nephrol* 1999;125:159-72.
- 35Fischbach M, Terzic J, Laugel V, Dheu C, Menouer S, Helms P, Livolsi A. Daily on-line haemodiafiltration: a pilot trial in children. *Nephrol Dial Transplant*. 2004; 19(9): 2360-7.
- 36Fischbach M, Terzic J, Menouer S, Dheu C, Soskin S, Helmstetter A, Burger MC. Intensified and daily hemodialysis in children might improve statural growth. *Pediatr Nephrol* 2006;21:1746-52.
- 37Kari JA, Rees L. Growth hormone for children with chronic renal failure and on dialysis. *Pediatr Nephrol* 2005;20:618-21.
- 38Boehm M, Riesenhuber A, Winkelmayer WC, Arbeiter K, Mueller T, Aufricht C. Early erythropoietin therapy is associated with improved growth in children with chronic kidney disease. *Pediatr Nephrol* 2007 Mar 30; [Epub]
- 39Koda Y, Nishi S, Miyazaki S, Haginoshita S, Sakurabayashi T, Suzuki M, Sakai S, Yuasa Y, Hirasawa Y, Nishi T. Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. *Kidney Int* 1997;52:1096-101.
- 40Nakai 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.
- 41Locatelli F, Manzoni C, Di Filippo S: The importance of convective transport. *Kidney Int Suppl*. 80:115, 2002
- 42Lornoy W, Becaus I, Billioux JM, Sierens L, Van Malderen P, D'Haenens P. On-line haemodiafiltration. Remarkable removal of beta2-microglobulin. Long-term clinical observations. *Nephrol Dial Transplant* 2000;15 Suppl 1:49-54.
- 43Eknoyan G, Beck GJ, Cheung AK, *et al.*: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 19:347, 2002
- 44Canaud 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;69:2087-93.
- 45Jirka 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;70:1524.
- 46Bosch 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.
- 47Maduell F, Navarro V, Torregrosa E, Rius A, Dicenta F, Cruz MC, Ferrero JA. Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. *Kidney Int* 2003;64:305-13.
- 48Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, Nube MJ, ter Wee PM; CONTRAST Group. Resolving controversies regarding hemodiafiltration versus hemodialysis: the Dutch Convective Transport Study. *Semin Dial* 2005;18:47-51.
- 49Canaud 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-S12.

Correspondence to:

Prof. Bernard Canaud
Nephrology, Dialysis and Intensive Care.
Lapeyronie University Hospital
371, Avenue du Doyen Gaston Giraud
34295 Montpellier Cedex 5
France
E-mail: b-canaud@chu-montpellier.fr