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On-line Hemofiltration in Chronic Renal Failure: Advantages and Limits

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Sardinian Co-operative Study Group on Hemofiltration on-line (*)

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(*) The other members of the Study Group are listed in the Appendix.

Introduction

The actual dialysis therapy offers a notable long-term survival and rehabilitation, but it is still far from normalizing the patient's quality of life as well as mortality and morbidity.[1]

The most widely used dialysis therapy is an almost exclusive diffusive treatment performed with low-flux cellulose membranes with a dialysis dose targeted to a urea Kt/V of 1.2 or higher.

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The convective treatments, which use high-flux membranes, offer proven biological superiority over diffusive treatments, which are performed with bio-incompatible, low-flux membranes. Retrospective epidemiological studies have documented a reduction of morbidity and mortality with the use of high-flux membranes, but the results of the prospective studies comparing low-flux with high-flux treatments are still conflicting.[2,3]

Cardiovascular instability during treatment sessions is a potential cause of morbidity and mortality for patients on dialysis treatment.[4] Hemofiltration (HF) is a pure convective treatment and offers the best tolerance to fluid subtraction in hemodynamically unstable patients.[5,6] Because of its limitation in removing urea as well as

high costs, HF treatment is restricted to few high risk unstable patients. The modern pre-dilution HF, performed with ultrapure on-line prepared solutions, overcomes, at least partially, the above limitation,[7,8] but there is scarcity of data evaluating its long-term efficacy in stable patients.

Material and Methods

A Sardinian Collaborative Group, comprising ten dialysis units, has been studying on-line HF since 1995. The group carried out two prospective collaborative trials and a third trial is on going.[9,10] The aims of the above studies are to compare different treatments performed with different doses of convection in hemodynamically stable patients, to establish if convection, and in what dose, is effective in improving the patient's symptoms and stability during treatment sessions and between treatments.

Study design: methods

The following experimental design was common in all our studies:

a) The monitors used in all studies were the AK100 or 200 Ultra from Gambro AB, that prepare on-line ultrapure dialysis fluid obtained by reverse osmosis treated water, dry bicarbonate cartridge (BiCart) and a series of three ultrafilters which guarantee the high bacteriological quality for hemodialysis (HD), hemodiafitration (HDF) and HF treatments.

b) The same fluid electrolyte concentration (mmol/l) was used for HD, HDF and HF: Sodium 138-140; potassium 1-2; chloride 108.0-109.5; calcium 1.50-1.75; magnesium 0.5; bicarbonate 30-34; acetate 3.0 and glucose 0-5.55 (all mmol/L).

c) Dialyzers and hemofilters were all poliamide filters (Poliflux 14, 17, 21 Gambro AB).

d) Selection of patients was done using the following criteria: stable clinical condition; urine output $\leq$ 300 ml/day; absence of chronic infection, malignancy, diabetes, liver insufficiency or active liver diseases, serious endocrine dysfunction or vascular diseases; well functioning vascular access; and body weight $\leq$ 85 kg.

e) Clinical, hematological and adequacy monitoring and treatment parameters*:* during each session, the following parameters were recorded: Qb infusion flow rate (Q_{inf}); rate of weight loss, total infusion volume, treatment time and composition of dialysis and substitution fluids.

Clinical parameters including body weight, blood pressure (BP), heart rate and body temperature were monitored before and after each treatment.

f) Intra-treatment symptoms: the number of episodes of symptomatic hypotension and hypertension, cardiac arrhythmia, dyspnea, fever, muscular cramps, headache, pruritus, nausea and vomiting were recorded during each treatment.

g) Inter-treatment symptoms. The patients were asked to record the presence of the following symptoms experienced during the inter-treatment periods: hypotension, hypertension, arrhythmia, respiratory distress, fatigue, abnormal thirst, diarrhea and constipation, insomnia, arthralgia, nausea and vomiting.

h) Urea kinetics. The urea kinetics were determined at the beginning of each treatment phase and every two weeks subsequently during the mid-week session. Pre-(C1) and post-(C2) session urea concentration were determined in blood samples taken from the arm contralateral to the fistula. The sample for post-session urea (C2) was taken 30 minutes after the end of the treatment. Equilibrated Kt/V (eKt/V) and equilibrated normalized protein catabolic

rate (nPCR) were calculated using the Daugirdas formula.[11] These formulae are validated for multi-compartment variable-volume modelling for HD.

Clearances. *In vivo* plasma urea and creatinine clearances were determined at least twice during each treatment phase.

i) Blood analysis. A full blood analysis was carried out every second week from samples taken before the first treatment of the week.

j) Infusion therapy and drugs. Intravenous plasma-expanders and/or hypertonic saline administration per session was recorded. The list of drugs taken during the inter-treatment period was also registered.

Peculiarities of the three different studies

The first study: Twenty-three patients were initially treated on high-flux HD for three months, and subsequently by pre-dilution HF for six months. The Kt/V was aimed differently in the two treatments (1.0 on HF and 1.4 on HD). The treatment time was also different.[9]

The second study: Twenty-four patients received three different modes of treatment successively, each mode lasting six months: pre-dilution HF, high-flux HD, pre-dilution hemofiltration (HF2). In all three phases, the same Kt/V and the same treatment time were used.[10]

The third study: Forty-two patients were started initially on treatment with low-flux HD for six months. Then the patients were randomized to receive either treatment A; on-line pre-dilution HF; or treatment B; pre-dilution on-line HDF, with an infusion volume of about the 50% of the flow blood rate (Qb).[12]

At the end of six months of treatment, all patients who received treatment A were crossed over to treatment B and vice versa. The study will end in October 2001.

Satellite studies

The β-2-microglobulin levels were calculated at the beginning and end of each phase of treatment.

Ambulatory blood pressure monitoring (ABPM) was determined using Space-Lab device during 48 hours, midweek. The continuous monitoring began at the end of the first treatment of the week and lasted for 48 hours. This procedure was carried out in the middle of the second and the third phases of the second study.

Estimation of the bio-electrical impedance: Resistance (Rx) and reactance (Xc) parameters were measured in all three phases of the second study at the end of the sessions. Body composition was evaluated by single frequency instrument (50 KHz, BIA-101 Akern/RJL, Florence).

Quality of life: All patients were submitted to a quality of life test in the middle of each phase of the second study.

Statistical analysis

The Student's t-test was used for paired data. Significance was defined as a p value < 0.05 level.

Definitions

A hypotension episode was defined as a symptomatic fall in the values of the systolic blood pressure by 20 mm Hg or more, requiring saline or plasma-expander infusion during sessions, or a change in the therapeutic schedule inter-treatment.

A hypertension episode was defined as a symptomatic rise in the values of the systolic blood pressure above 160 mm Hg, with an increase by 20 mm Hg or more above the basal values, requiring therapeutic intervention.

Table 1. Adequacy and nutritional parameters.

	HF1	*HD*	*HF2*	*p*
Equilibrated Kt/V	1.25	1.28	1.26	n.s.
Equilibrated nPCR	1.16	1.10	1.12	n.s.
Urea reduction ratio, %	64.66	65.01	64.86	n.s.
Dry weight, (Kg)	55.06	54.62	55.83	n.s.
Inter-session weight gain, (Kg)	2.4	2.6(*)	2.4(*)	<0.01
Albumin, g/L	3.6	3.7	3.6	n.s.
Pre-session plasma bicarbonate, (mEq/L)	22.8(*)	21.9(*)	22.3	<0.05

The results of the Sardinian collaborative studies

Table 1 shows the results of the comparative urea kinetics and some relevant laboratory features of the second study.

The Kt/V was significantly higher on HD in the first study (HD: 1.41 ± 0.26, HF: 1.08 ± 0.19; p<0.001) (9) while it was similar in the second study as targeted (10). The nPCR generation was similar in all phases of both studies, and no correlation was found between Kt/V and nPCR parameters. The ratio obtained by dividing Kt/V by PCR values was higher on HF than HD in the first study, while it was similar in the second study.

Body weight and serum albumin did not vary significantly during the two studies, but the dry weight (post-dialysis weight) was higher, although not significantly, during HF in the second study. The weight gain was significantly higher on HD in the second study. Pre-dialysis serum bicarbonate was better corrected by HF in the second study

Symptoms during treatments and in the inter-treatment period

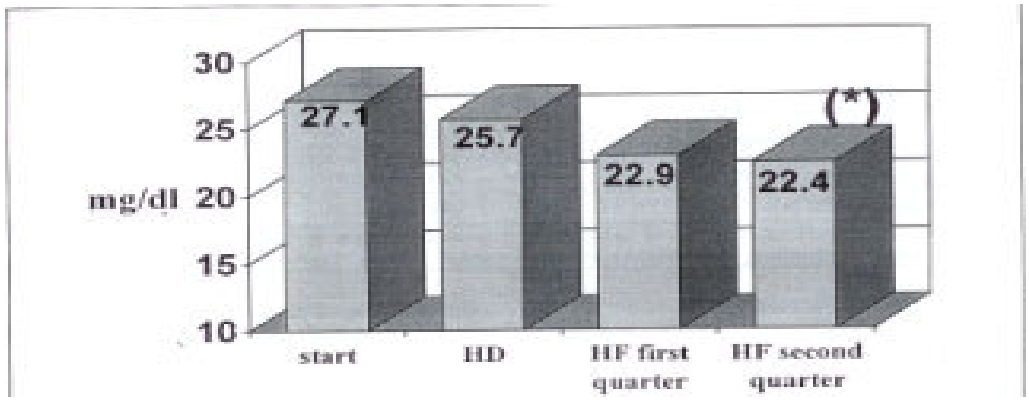
Patients experienced less symptoms during HF than HD sessions (Tables 2 and 3). The prevalence and the frequency of the hypotensive episodes and muscular cramps was lower during HF than HD, in both studies. The score obtained by the sum of the prevalence of symptoms commonly related to the treatment, was significantly lower during HF than HD, as it was in the inter-treatment period.

In particular, during the interval between treatments, patients experienced less fatigue and muscular cramps when they were treated with HF.

Table 2. Symptoms during session: average monthly.

	First study			Second study		
	HD	**HF**	p	**HD**	**HF**	p
Prevalence of patients with hypotension, %	61	39	0.03	66.7	23.3	<0.01
Episodes of hypotension per patient	1.78	1.17	0.003	1.81	1.28	0.04
Prevalence of patients with hypertension, %	30	26	0.04	6.7	3.3	n.s
Prevalence of patients with muscular cramps, %	33	17	0.003	26.7	6.7	0.03
Prevalence of patients with nausea and vomiting, %	17	4	0.02	6.7	4	n.s.
Sum of prevalences (*), %	141	86	0.02	107	37	0.03

(*) The sum of prevalence is given to: arrhythmia + pruritus + fever + dyspnea + muscular cramps + headache + nausea + vomiting.



*** p=<0.03**

Figure 1. Pre-session levels of β-2 microglobulin (first study).

ß-2 Microglobulin

The pre-treatment *ß*-2-microglobulin levels, determined in the first study, decreased progressively through the two phases of treatment with a significant reduction at the end of HF treatment period (Figure1). This confirmed the enhanced *ß*-2-microglobulin clearance with pre-dilution HF.[13]

Quality of life

Figure 2 shows that the patients' quality of life determined in the second study did not vary significantly during HF and HD treatments.

Bio-electrical impedance

The body reactance values determined in the second study were significantly lower during the HF period (HF1 38 ±15; HD 46 ±12; HF2 38 ±12; Ohm/sm; p<0.01).

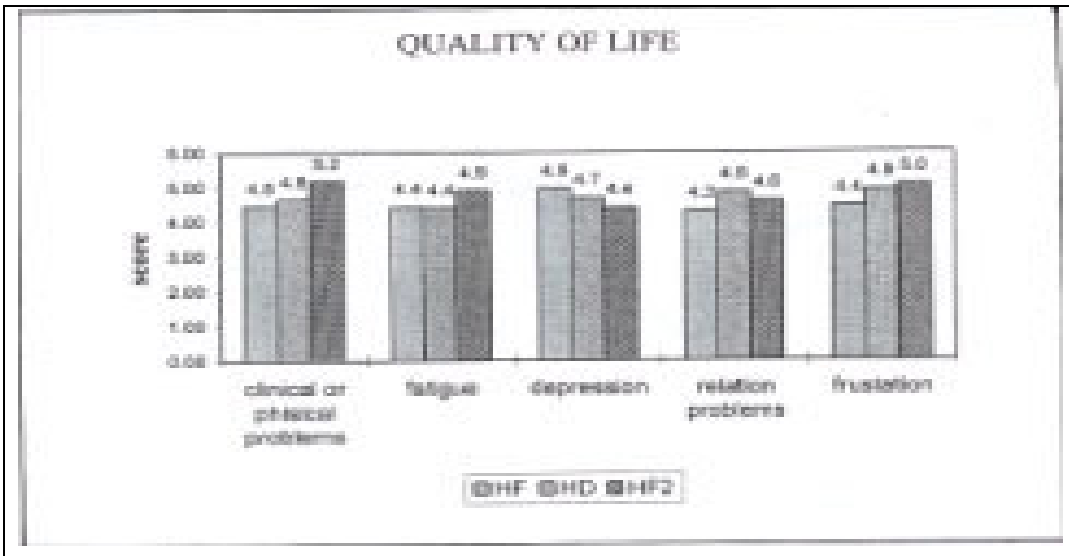


Figure 2. Quality of life.

Table 3. Symptoms in the inter-session period: average monthly.

	First study			Second study		
	HD	**HF**	p	**HD**	**HF**	p
Prevalence of patients with hypotension ,%	9	11	n.s	30	10	<0.01
Prevalence of patients taking any anti-hypertensive medication, %	48	37	0.03	33	26	n.s.
Prevalence of patients with muscular cramps, %	22	13	0.03	13	0	n.s.
Prevalence of patients with fatigue, %	59	24	0.01	26	3	0.04
Sum of prevalences (*), %	90	48	0.03	30	13	0.04

(*) The sum of prevalence is given to: arrhythmia + pruritus + fever + dyspnea + muscular cramps + headache + nausea + vomiting + arthralgia + insomnia + thirst.

Cardiovascular monitoring

Table 4 depicts the blood pressure recording in the second study. The number of nocturnal dippers, defined as patients with a fall in BP $\geq$ 10% of the 24 hour values was low (1 out of 15 on HF, 2 out of 15 on HD); the number of patients taking anti-hypertensive drugs was lower, but not significantly, during HF than HD. The mean blood pressure values, determined pre- and post-session, were higher on HF than HD in the second study.

The outcome of daytime and night-time systolic and diastolic blood pressure measured by ABPM showed a better effect in the HF periods.

The hypotension episode frequency was not constant, but varied through the second study, as indicated in Figure 3. The frequency increased progressively during the HD period and decreased during the subsequent period of HF. Similar was the outcome of blood pressure values, (pre- and post-session), which dropped progressively during HD treatment period and rose progressively during HF treatment (Figure 4).

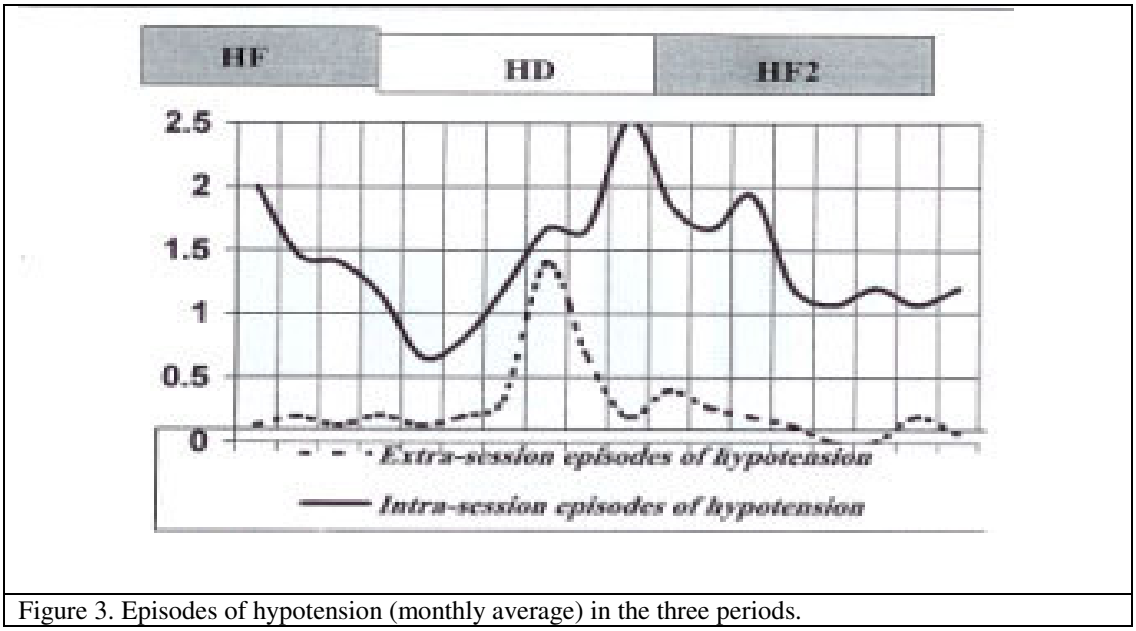


Figure 3. Episodes of hypotension (monthly average) in the three periods.

Table 4. Pre and post-session blood pressure, inter-session weight gain, ultrafiltration per hour, arterial blood pressure monitoring (ABPM)

	HF1	**HD**	**HF2**	***p***
PRE-SESSION systolic blood pressure, mmHg	135.8(*)	128(*)	130	0.028
POST-SESSION systolic blood pressure, mmHg	125.9(*)	117(*)	122	0.02
Inter-session weight gain, Kgs	2.4	2.6(*)	2.3(*)	0.014
Ultrafiltration per hour, % of body weight	1.43	1.49	1.42	n.s.
INTER-SESSION PERIOD				
Average 24-hour systolic blood pressure, mmHg		113,9.	118.5	0.001
Average daytime systolic blood pressure (ore 7 – 22), mmHg		114.4	121.1	0.001
Average daytime diastolic blood pressure (ore 7 – 22), mmHg		68.5	70.2	0.005
Average night-time systolic blood pressure (ore 22 – 7), mmHg		112.8	114.7	0.001
Average night-time diastolic blood pressure (ore 22 – 7), mmHg		65.3	62.7	0.07

Discussion

Safety and adequacy of on-line hemo-filtration

There were no febrile reactions or significant body temperature increase related to the technique, during over twenty thousand treatments performed in our studies. Previous reports have shown that adequate PCR levels can be reached with a lower Kt/V if more compatible membranes are used.[8] Our first study confirmed that the same good nutritional status generating similar PCR values, was reached in the same patients while they were treated on HD, at a Kt/V value of 1.00;[9] this dose is considered not adequate for standard dialysis treatment. Urea removal is no longer a limitation of modern HF, except for the very larged-sized patients. In our experience, only a single patient suspended the HF treatment, during the study I, because of very elevated urea values due to dietetic non-compliance. The above observations and experience with on-line HF, indicate that HF is a safe and therapeutically adequate procedure.

Substantial clinical differences observed during HD and HF

Our experience, confirmed that HF offers a better cardio-vascular stability reducing the frequency of episodes of hypotension during treatment sessions. Furthermore, patients during all phases of HF treatment, experienced significantly less symptoms during the inter-treatment period, in particular less fatigue and muscular cramps.

Our studies showed a significant reduction of intra-treatment hypertension episodes and a reduction, although not attaining statistical significance, of the number of patients needing any anti-hypertensive treatment.

The ambulatory blood pressure monitoring (ABPM), carried out in the second study, confirmed the very low prevalence of hypertension in both treatments (0 patients on HF and 1 on HD), and showed a tendency for patients to have a more physiological cardiovascular response during hemofiltration. The blood pressure profile was slightly higher on HF than HD. Furthermore, the dipping tended to be more physiological on HF.

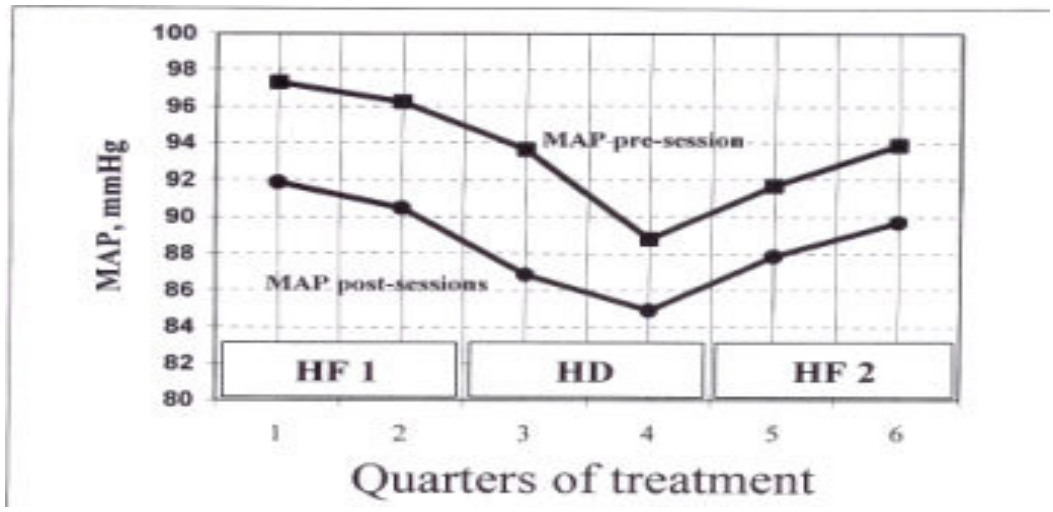


Figure 4. Pre and post-session outcome of mean arterial pressure (MAP): second study.

Acidosis was better corrected in patients on HF, during the second study.

What was the reason(s) for the better response of patients to HF than HD?

At the present it is not possible to establish which factor/factors are responsible for the better cardiovascular stability on HF.

The present studies exclude the possibility that the better tolerance offered by the HF treatment was due to a better biocompatibility, since the membranes, the fluid composition and the fluid quality were the same in both treatments.

Usually HF treatments are targeted to a Kt/V which is lower than HD, a factor that can potentially cause a different cardiovascular response. In our second study, the urea removal indices were similar in the two treatment modes, with a target Kt/V of 1.2 in both. Consequently, a slower solute removal was not the cause of the better cardiovascular tolerance on HF.

Maggiore[14] attributed the better stability on HF to the greater lowering of the body temperature by HF than HD. This finding was confirmed by more recent studies which found that the stabilizing effect observed during treatments on HF may be neutralized by avoiding the temperature lowering during HF sessions by warming the infusion fluid.[15] A simple thermal effect could explain the better blood pressure stability and the less symptomatic sessions, but it is an unlikely cause of the steady improvement of the patient's symptoms, that persists between treatments, particularly fatigue and cramps.

Furthermore, the frequency of hypotension episodes during treatments (Figure 3), had a progressive change during each phase. This indicates that the stabilizing effect of the HF treatment was progressive and long-term rather than acute, as has previously been described.

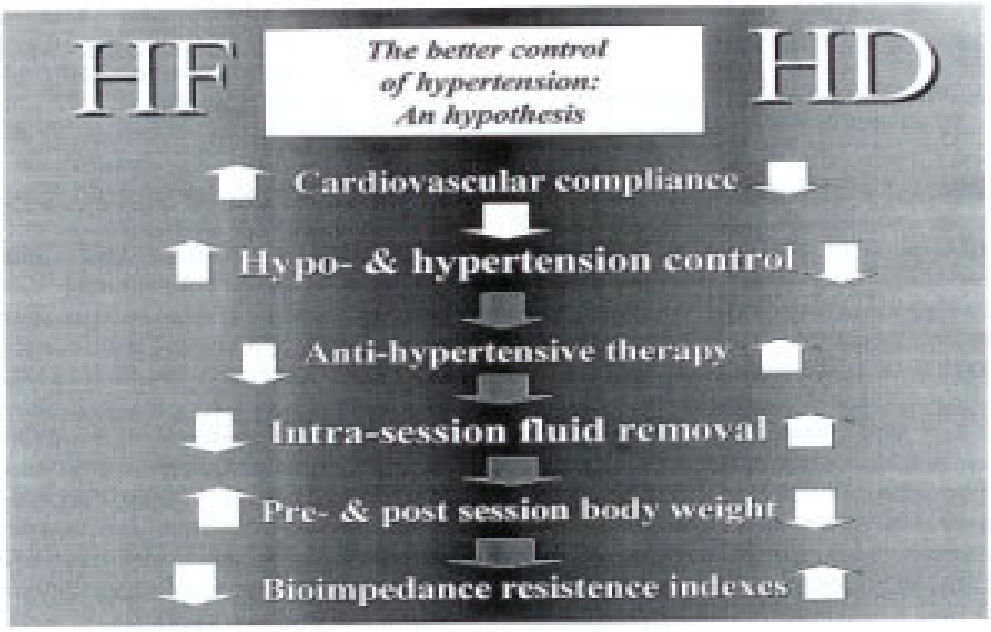


Figure 5. The hemofiltration is able to improve the cardiovascular stability: a hypothesis.

The different pattern of bio-electrical impedance during HF and HD, in the absence of significant changes of the dry weight, deserves further comments.

The hypothesis that HF leads to a retention for sodium and water, caused by a reduced sieving coefficient for sodium due to convective transport, could be compatible with our findings of bioimpedance which showed that the same patients were less dehydrated after HF than HD sessions. Moreover, the mean patients' body weight was higher although not significantly and their blood pressure levels slightly more elevated on HF than on HD.

This finding is apparently in contrast with the very good blood pressure control, the lower inter-treatment weight gain, the lower prevalence of patients needing anti-hypertensive drugs, and the tendency to a more physiological dipping present in our patients while they were treated on HF.

A possible explanation of the above contrast could be a better cardiovascular compliance offered by the HF treatment, which allows the patient to tolerate a higher sodium and water retention without generation of hypertension, and, on the other hand, the need to dehydrate more patients to keep them normotensive while they are being treated by HD (Figure 5).

Therefore, at the moment, it is unlikely to ascribe the different patient's response to HF and HD to a single phenomenon because of the different spectra of solute removal caused by convective and diffusive treatments and the various potentially different technical conditions present during HF and HD treatments.

Are the advantages of on-line HF over HD relevant enough to justify a more widespread use of HF?

The main limiting factor of modern HF is cost related to the technique, since a single session of on-line pre-dilution HF costs in our centers, 2.5 times that of the cost of a session of low-flux cuprophane HD. Although cost is a relevant problem, we have to consider the future of our patients, and that dialysis therapy is still far from being perfect treatment. Patients' morbidity and mortality on maintenance dialysis is considerably higher than that of the normal population,[17] and transplantation offers a considerably longer survival than HD.[18]

Convective treatments offer a proven biological superiority over diffusive treatments. Recent epidemiological studies have found a reduction in the incidence of carpal tunnel syndrome and a tendency to reduction in the patient's mortality with convective treatments.

What dose of convection and what kind of convective treatment may offer the best protective effect is still an open question.

Many prospective trials[19,20] did not find a difference between subjective and objective symptoms during and after HD using low or high-flux biocompatible membranes and cellulosic membranes.

Also, the hemodiafiltration treatments were not able to improve cardiovascular stability in the many prospective studies.[21]

At the moment, it is not possible to make a comparison between on-line HF and on-line HDF treatments, since no prospective studies on the subject have been published. At the present, only prospective studies comparing HDF with standard HD are available, but their results did not show a clear improvement of patients' cardiovascular stability.

In a recent prospective study,[20] 44 patients were randomized to receive on-line low-flux HD or on-line HDF. The same membrane (polysulphone), fluid composition, ultrapure fluids, and the same Kt/V (1.8) were used in both treatments.

β-2-microglobulin values diminished significantly after six months of HF, and remained stable thereafter. Intra-dialysis hypotension episodes, body weight and bioimpedance values did not differ significantly in the two groups.

Hemofiltration has its principal indication for treatment of patients with cardiovascular instability, and our studies demonstrated that HF offers a better cardiovascular stability and is less symptomatic even in stable patients.

If large-scale prospective and randomized trials confirm a clear superiority of convective treatments in reducing the patient's mortality, we will have to consider that HF is the treatment that offers the highest dose of convection.

Our studies did not include a sufficient number of patients for epidemiological analysis, but add and further confirm that the use of on-line pre-dilution HF is capable of obtaining a sufficient urea removal while keeping the treatment times not substantially different from HD, with proven clinical benefits for patients.

Appendix

The following investigators participated in the Sardinian Co-operative Study Group on Hemofiltration on-line. Sardinia-Italy. E. Asproni (Nuoro), GF. Cabiddu (Cagliari), L. Calvisi (Ozieri), D. Casu (Alghero), B. Contu (Lanusei), L. Gazzanelli (La Maddalena), A. Ginanni (Alghero), T. Ghisu (Macomer), R. Ivaldi (Oristano), S. Murtas (Quartu Sant' Elena), M. Passaghe (Tempio Pausania), I. Pillosu (Cagliari), M. Pinna (Sassari), A. Piras (Alghero), R. Pistis (San Gavino Monreale), G. Sau (Cagliari), G. Serra (Sassari), R. Solinas (Sassari), E. Sulis (Lanusei).

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