SEDYT, VII/4, 99-106 (1985)

Single needle hemodiafiltration

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Introduction

In conventional hemodialysis, solutes are predominantly removed by a diffusion process, whereby uremic toxins migrate from the patients blood towards the dialysate due to a concentration gradient. This method is especially suitable for the elimination of small molecular substances.

In 1967, Henderson and his coworkers introduced hemofiltration as an alternative to conventional dialysis, especially in the treatment of overhydrated uremic patients (1). This technique consists of an elimination of toxic products by a convective process; body fluid that contains toxins is eliminated by rapid ultrafiltration and substituted by an isotonic saline solution. With this method, the elimination of middle molecules is theoretically better, but the clearance of small molecules will be less adequate than with conventional dialysis. For that reason, hemodiafiltration was proposed as a third alternative in 1978 by Leber and colleagues (2). This method combines the advantages of both conventional dialysis and hemofiltration in one and the same technique; this results in diffusion and convection, or in other word, in an elimination of small as well as of larger molecules. As long as the role of biological toxicity of all the known and unknown uremic molecules remains undefined, it seems appropriate to pursue the non specific elimination of uremic toxins of both smaller and larger size. Subsequently, hemodiafiltration might be the ideal compromise for the treatment of the uremic state.

In the literature, multiple advantages have been attributed to the hemodiafiltration technique. First, a better hemodynamic tolerance, compared to conventional dialysis, has been claimed (3). Second, clearances of both small and larger molecules are higher with hemodiafiltration (4). Third, many of the filters currently used for the hemodiafiltration technique, have a chemical structure that allows a better biocompatibility than that observed in conventional dialysis (5).

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Technical equipment

We started hemodiafiltration in our Unit in 1978. The original indication was vascular instability. With time, however, other indications were added to this, as will be illustrated later.

A flowchart of the technical set-up that is regularly used in our patients on hemodiafiltration is shown in fig. 1. The ultrafiltered volume is substituted by an electrolyte containing solution in the post-dilutional mode. For the rest, this set-up is entirely the same as the one used in conventional hemodialysis. The composition of the substitution fluid is 140 mEq/L of Na^+, 1 mEq/L of K^+, 3.75 mEq/L of Ca^{++}, 1.5 mEq/L of Mg^{++}, 101 mEq/L of Cl^- and 45.5 mEq/L of lactate.

In table I, the filters are mentioned that are used or have been used in our Unit for the hemodiafiltration technique, together with their characteristics. We use most often polyacrylonitrile (AN69) membranes. The large majority of our patients are now on Biospal 3000 S. The present data mostly will refer to these filters, unless otherwise stated.

In this introduction, one question still remains to be answered: why *single needle* hemodiafiltration? All our patients without any exception are treated with the single needle method. The single needle method is especially suited for this hemodiafiltration, because of it's basic prin-

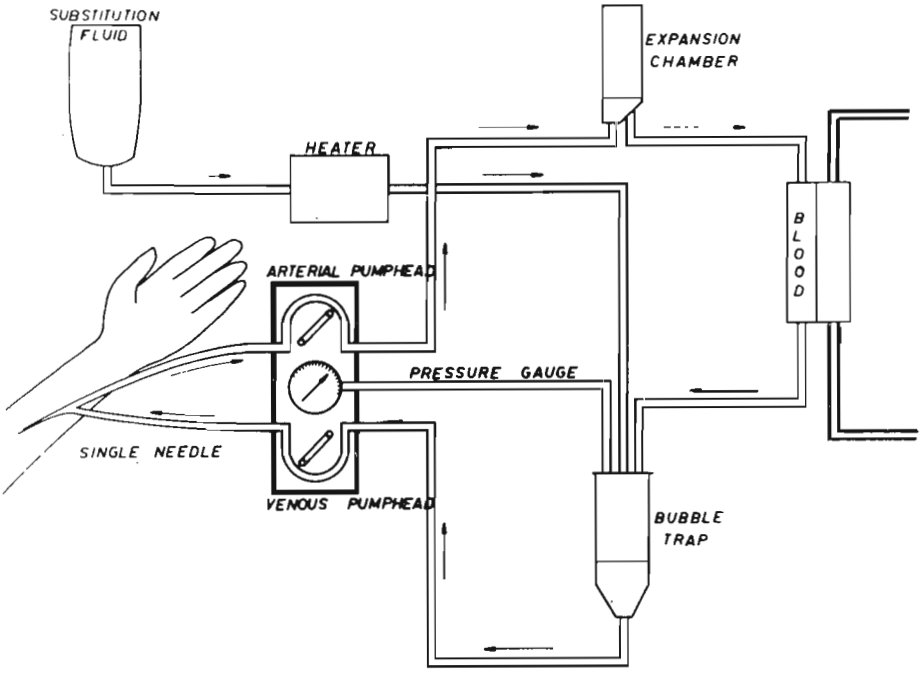

Fig. 1. Flow-chart of the technical set-up.

TABLE I

Hemodiafiltration: filters used

Hemodiafilter	Material	Surface	Type
FILTRAL 7 + 8	AN 69	1.0	Plate
BIOSPAL 3000 S	AN 69 S	1.2	Plate
Cordis Duoflux	Cellulose acetate	1.8	Hollow Fiber
Gambro High Flux	Cuprophane	1.7/1.36	Plate
Filtryzer B_I	PMMA	1.15	Hollow Fiber
Filtryzer B_IL	PMMA	2.1	Hollow Fiber
Asahi 150	PAN	1.0	Hollow Fiber

ciple of pressure-pressure monitoring, which allows a good ultrafiltration control. The principle of increasing pressure in the blood compartment of the dialyzer to increase the ultrafiltration appears to be more physiological or biological as related to the human glomerules, than the «hemo-suction» exerted by creating a negative pressure on the dialysate outflow.

With the single needle technique, an ultrafiltration volume of 10 liters plus the interdialytic body weight gain can be obtained easily without increasing the average TMP above 300 mmHg. This results in a virtually linear evolution of the cumulative ultrafiltered volume over the entire duration of the hemodiafiltration session.

Dialysis tolerance

Hemodynamic tolerance

Pre- and post-dialysis mean arterial blood pressures, as well as the highest and the lowest registered blood pressure of each dialysis session were averaged in 16 patients in good cardiovascular condition (fig. 2). They were treated consecutively by conventional dialysis and hemodiafiltration. The follow-up period covered a mean number of 69 sessions per patient with either technique. The ultrafiltration volume was similar in both groups. No significant differences in blood pressure were observed.

For the same series of hemodialysis and hemodiafiltration sessions, the number of hypotensive and hypertensive episodes was compared. Hypotensive episodes were defined as a symptomatic blood pressure fall or a decrease by at least 50 mmHg. We observed no significant difference between both techniques (table II). Hypertensive episodes were defined as a rise of diastolic blood pressure to 95 mmHg or more; here, the number of events was slightly but significantly lower with the hemodiafiltration technique (table II).

Clinical tolerance

The number of dialysis sessions complicated by vomiting, headache and muscle cramps were registered and are illustrated as a percentage in

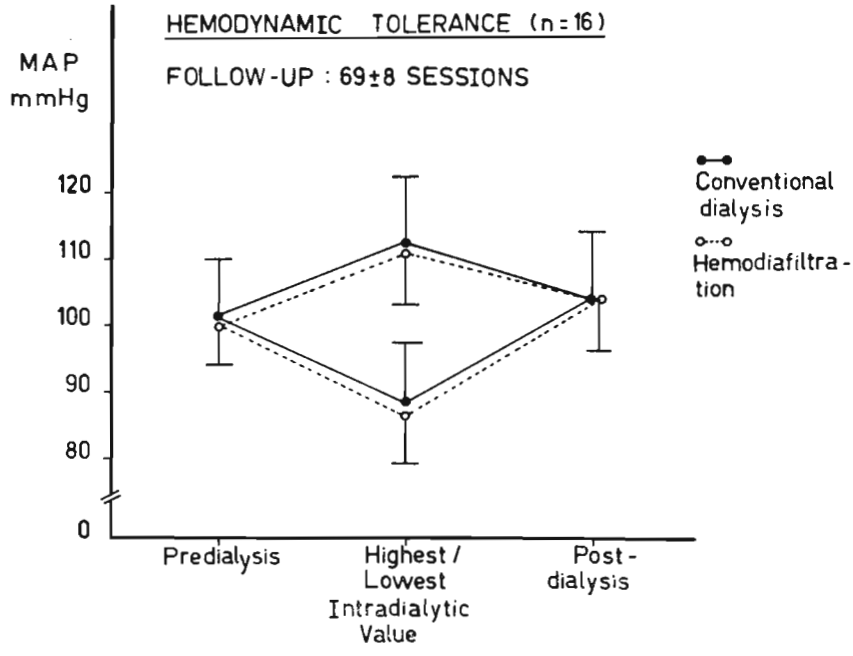

Fig. 2. Mean values of pre- and postdialysis and of the highest and the lowest intradialytic mean arterial blood pressure in 16 patients, treated consecutively with conventional hemodialysis (full line) and with hemodiafiltration (broken line). No significant differences were observed.

table III. All these complications were less frequent with the hemodiafiltration technique; they were already very low with conventional single needle dialysis. Subsequently, blood pressure evolution was rather similar in our hands, both with conventional dialysis and hemodiafiltration. However, hemodynamic tolerance is already surprisingly good in our conventional program, as also stated by us at the EDTA Congress in Florence last year (6). The number of hypotensive episodes was somewhat lower with hemodiafiltration. On the other hand, clinical complications were lower with hemodiafiltration. It should be stressed that the present data are retrospective and thus should be interpreted with care. We are planning a prospective study in the near future.

TABLE II

Number of hypo- and hypertensive episodes

	Conventional Hemodialysis	Hemodiafiltration
Hypotension (%)	1.5	1.3
Hypertension (%)	4.7	2.7 **

** : $p < 0.01$

TABLE III

Clinical tolerance

	Conventional Hemodialysis	Hemodiafiltration
Nausea (%)	1.8	1.4
Vomiting (%)	5.7	2.6 **
Headache (%)	2.9	0.6 **
Cramps (%)	5.7	4.2 *

* : $p < 0.05$
** : $p < 0.01$

General clinical condition

The general status of our patients was evaluated using a 10 point scoring index. Five points were alloted for clinical status, 1 point for a blood pressure under control, 1 point for a hematocrit equal to or greater than 30 %, 1 point in case of good social rehabilitation, 1 point if the nerve conduction velocity at the fibular site was 40 m/s or more, and 1 point if the Hepatitis B Ag was negative or the Hepatitis B Ab was positive. In conventional dialysis, the scoring index was 7.0 points, compared to 6.8 in hemodiafiltration.

Evolution of the nerve conduction velocity was considered separately as illustrated on the left panel of fig. 3. Expressed as m/sec, it was measured externally with a Neurodial-apparatus. No significant differences were observed. The right panel shows the average hematocrit in both

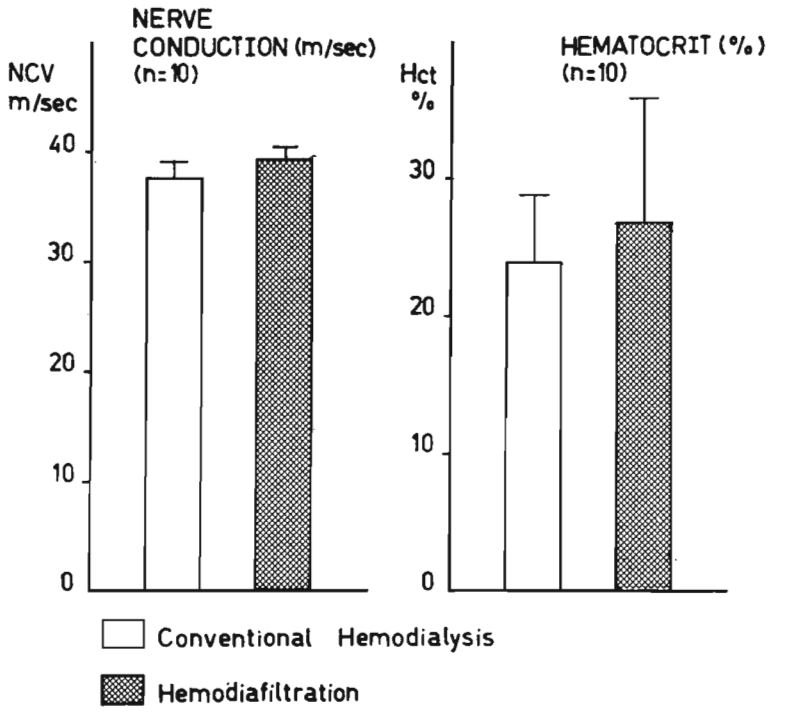

Fig. 3. Mean nerve conduction velocity (left panel) and hematocrit (right panel) during conventional hemodialysis (open bars) and hemodiafiltration (hatched bars).

groups. Only patients that needed no blood gifts during the study were considered. Although the hematocrit of the patients on hemodiafiltration is some 11 % above that of the patients on conventional dialysis, the differences are not statistically significant.

One specific point deserving consideration, is the reactivity to hepatitis B vaccination. Vaccination was obtained by the intramuscular injection of 1 ml of alterated hepatitis B antigen from the Pasteur Institute in France, and was injected intramuscularly every month during the first three months of the administration, followed by a fourth and fifth injection after 6 and 12 months respectively. Sufficient data have been obtained to enable a comparision 1, 2 and 3 months after the start of the vaccination.

Hepatitis B antibody was considered to be positive if a titer of 10 mU/ml or more was obtained. A significantly better reactivity was obtained in the group treated with hemodiafiltration after 3 months since about 80 % of the patients had a positive titer, compared to less than 50 % of the patients on conventional dialysis (fig. 4). It might thus be possible that a better removal of an inhibitor of the immune response was achieved with the hemodiafiltration method. Apart from the formation of hepatitis B Ab however, no parameter of clinical efficiency seems sensitive enough to allow any distinction between conventional dialysis and hemodiafiltration.

Biochemical parameters

In table IV monday pre- and post-dialysis serum concentrations of creatinine, and of several electrolytes in 10 patients are illustrated. No differences were observed.

A better estimation of dialysis adequacy is obtained by the calculation of urea kinetics as suggested by the American National Cooperative Study Group (7, 8). This method consists of two points: on one hand the time averaged urea concentration (TACUrea) is calculated, based on the pre- and post-dialysis serum urea concentrations obtained over a one week period. The second part of the calculation of urea kinetics consists of the determination of the protein catabolic rate (PCR), that has been shown to correlate directly with protein intake and urea generation rate. In the case of adequate dialysis, the time averaged concentration of urea should be 1.1 to 1.2 g/l, whereas the protein catabolic rate should be between 0.8 and 1.4 g/kg BW. day, the ideal value being 1.1. These values were determined in a large multicenter trial by the American National Cooperative Study Group and in the USA no dialysis strategy is accepted any more as adequate if these factors have not been calculated and proven to be within acceptable limits. It can easily be understood that TACUrea-levels can be appropriate in the case of inadequate dialysis, if protein intake and subsequently also protein

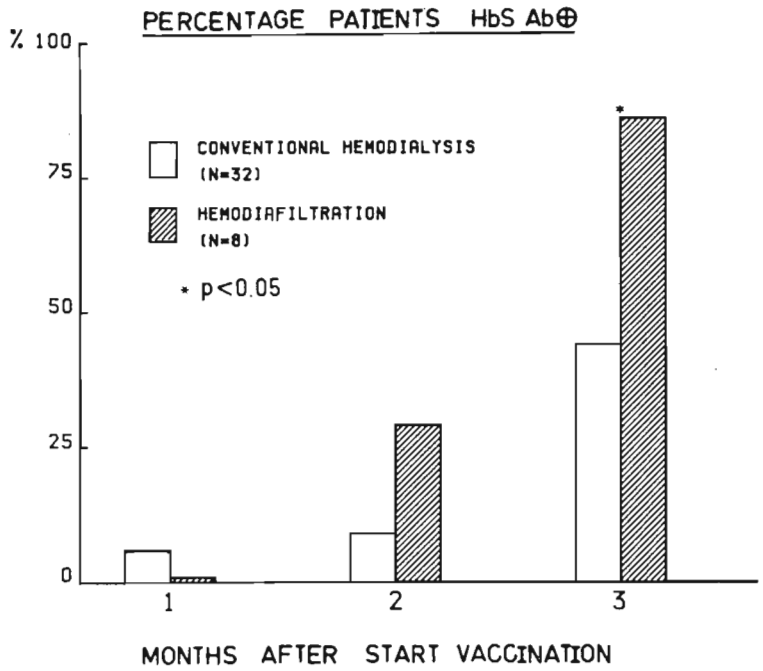

Fig. 4. Percentage of patients with a positive titer of hepatitis B antibody in conventional hemodialysis (open bars) and hemodiafiltration (hatched bars). * = $p < 0.05$.

TABLE IV

Biochemical data

		Conventional hemodialysis 360 sessions	Hemodiafiltration 360 sessions
Creatinine mg %	pre	12.6 ± 2.0	12.8 ± 2.0
	post	6.9 ± 1.7	6.6 ± 1.5
Urea g/l	pre	1.9 ± 0.4	1.8 ± 0.3
	post	0.8 ± 0.3	0.8 ± 0.2
K mEq/l	pre	5.7 ± 0.7	5.3 ± 0.6
	post	3.8 ± 0.5	3.4 ± 0.3
Na mEq/l	pre	138.1 ± 2.5	139.9 ± 1.7
	post	139.4 ± 2.2	140.9 ± 2.8
HCO_3^- mEq/l	pre	21.8 ± 2.2	22.0 ± 2.4
	post	24.6 ± 2.4	25.6 ± 3.0
Ca mg %	pre	9.4 ± 0.7	9.3 ± 0.6
P mg %	pre	6.1 ± 1.3	5.5 ± 1.5

TABLE V

Urea concentrations (g/l)

	Conventional dialysis	Hemodiafiltration
Monday		
Pre-dialysis	1.71 ± 0.32	1.69 ± 0.28
Post-dialysis	0.73 ± 0.19	0.77 ± 0.21
Wednesday		
Pre-dialysis	1.57 ± 0.34	1.56 ± 0.32
Post-dialysis	0.69 ± 0.23	0.73 ± 0.24
Friday		
Pre-dialysis	1.48 ± 0.36	1.48 ± 0.28
Post-dialysis	0.64 ± 0.19	0.62 ± 0.20

TABLE VI

Urea kinetics

	Conventional hemodialysis	Hemodiafiltration	Target values
TACurea (g/l)	1.14 ± 0.32	1.15 ± 0.24	1.10 to 1.20
PCR (g/kg, 24 hrs)	1.07 ± 0.31	1.10 ± 0.31	1.00 to 1.10

catabolic rate is too low, so that both parameters should be determined together to allow a correct estimation of dialysis adequacy.

In table V, the evolution of pre- and post-dialysis serum urea concentrations obtained over a one week period with both techniques is shown. There are no differences between conventional dialysis and hemodiafiltration. As can be appreciated from table VI, TACurea as well as PCR calculated from data obtained in patients treated with both methods, correspond to the values related to adequate dialysis in the American National Cooperative Study. Thus, these results pro-

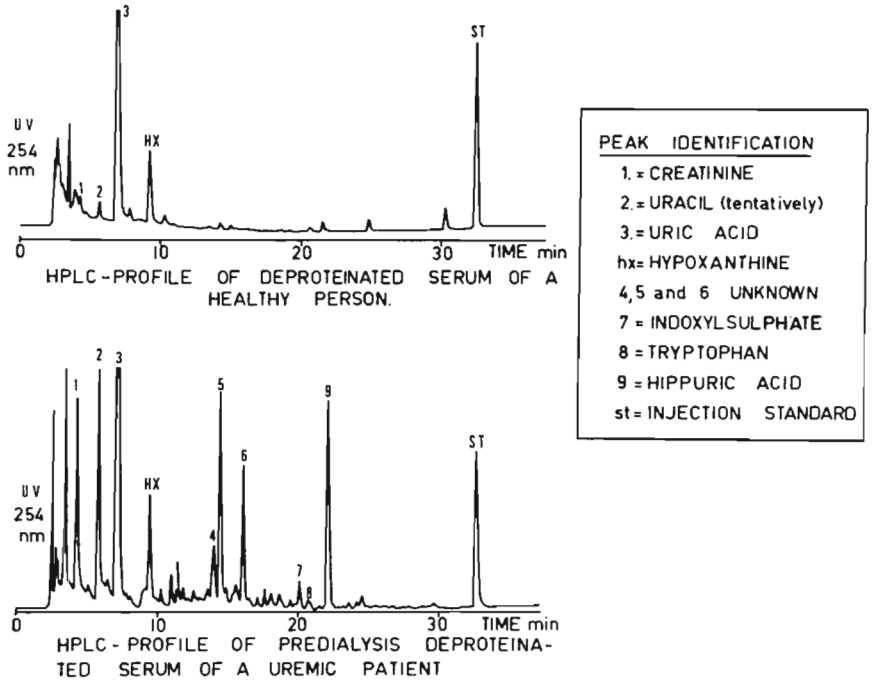

Fig. 5. HPLC-pattern of normal serum (above) and of predialysis serum of a terminal renal failure patient (below).

ve that blood purification with single needle pressure-pressure is adequate according to American Standards as well with single needle conventional dialysis as with single needle hemodiafiltration.

At this moment no superiority for hemodiafiltration over conventional dialysis is shown if based on «conventional parameters» such as urea or the more sophisticated protein catabolic rate and urea kinetics. But in our opinion, the determination of urea concentration is not entirely relevant as an estimation of uremic toxicity; so High Performance Liquid Phase Chromatography (HPLC)-studies of pre- and post-dialysis blood samples were performed, in an attempt to appreciate the elimination of other solutes apart from urea. For that purpose, the dialysis ratio was calculated for different solutes as an index for the efficiency of extraction (9).

In fig. 5, the HPLC-pattern of normal serum and of pre-dialysis serum of a terminal renal failure patient are compared. As could be expected, the number of recognisable peaks is substantially more pronounced in the dialysed patient, which corresponds to a greater retention of solutes in the blood. An attempt was made to identify these different peaks. We were able to define creatinine, uracil, uric acid, hypoxanthine, indoxylsulphate, tryptophan and hippuric acid. The eventual toxicity of these compounds remains a matter for debate. The important peaks 4, 5 and 6 remain unidentified. Studies are under way to characterize their chemical structure.

Fig. 6 shows a comparision of the dialysis ratio of these solutes during conventional dialysis and hemodiafiltration respectively. Here, with this HPLC method, for all solutes except tryptophan, the dialysis ratio was higher with hemodiafiltration than with conventional dialysis. This difference is significant for uracil, the unidentified peaks 4 - 6 and hippuric acid. The dialysis ratio of all Ultraviolet-absorbing solutes together was also higher for the hemodiafiltration technique. Thus, despite similar urea kinetics with both methods, the overall solute elimination appears to be better with hemodiafiltration than with conventional hemodialysis.

Specific indications

Our clinical experience could be summarized as follows: hemodiafiltration is an adequate dialysis technique; it is in many aspects at least as efficient as conventional dialysis; the technique is superior for the prevention of intradialytic hypertension, and dialysis intolerance.

Furthermore, solute elimination is better when determined by appropriate techniques. Subsequently, in our opinion, the use of a higher permeable filter seems indicated in therapy resistant hypertension, in any situation that should suggest an inadequate elimination of toxins, and in the case of bad dialysis tolerance, in the larger sense of the word.

If we look at our clinical experience of the

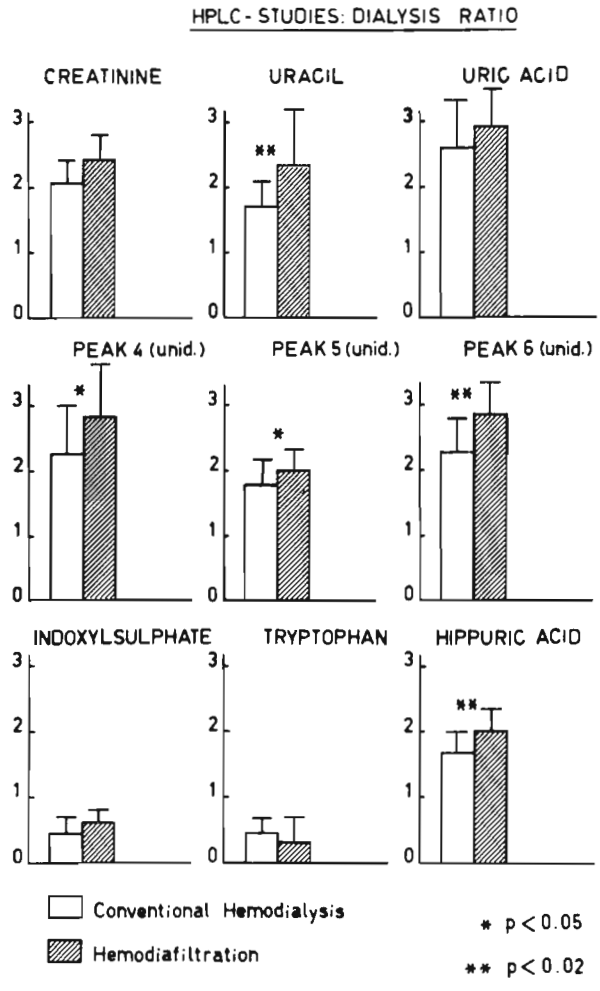

Fig. 6. Comparison of the dialysis ratio of different uremic solutes during conventional dialysis (open bars) and hemodiafiltration (hatched bars).

last year, the following problems were in our hands positively influenced by the start of hemodiafiltration: problems of clinical intolerance, treatment resistant hypertension, pulmonary insufficiency, therapy resistant itching and first use syndrome towards cuprophane.

One patient with pulmonary insufficiency did not react, but she had irreversible emphysema, in contrast to two other patients who developed bronchospasm each time that cuprophane dialysis was performed. One patient with diabetic neuropathy showed no objective improvement, probably due to the fact that irreversible damage to the nerves had occurred before.

Reprocessing

In view of some apparent advantages, the question arises as to why we didn't start hemodiafiltration in all our dialysis patients. The reason is economical, since the technique is rather expensive, both due to the cost price of the filters as such, but also of the substitution fluid.

Furthermore, the technique necessitates a more intensive nursing care, although the introduction of newer sophisticated technology has overcome this problem at least in part.

The question could be raised as to what extent polyacrylonitrile filters can be reused, in an attempt to diminish the costs of hemodiafiltration. We should first emphasize that reuse in our Unit is automated, which allows a standardized procedure and a quality control of the reused dialysers by means of a volume measurement and a pressure leak test. This method is limited to capillary dialyzers. The sterilant is formaldehyde. Since most of the polyacrylonitrile dialyzers that we use are plates, they cannot be taken into account for reuse in our program; so studies on the eventual feasability of reuse were undertaken with the Asahi 150 polyacrylonitrile capillary hemodialyzer.

It is shown in table VII that there is a quick and progressive deterioration of clearance function of these dialyzers after 6 reuses together with a parallel loss of the ultrafiltration capacity (table VIII). This experience contrasts with our general positive results with cuprophane dialyzers. The rejection of filters subsequent to an inadequate quality test also occurs faster with this polyacrylonitrile filter. Only 50 % of the polyacrylonitrile dialyzers are reused 6 times, whereas this figure is 90 % for cuprophane. Thus,

TABLE VII

In vivo urea clearances (ml/min - G_B : 200)

	1st use	3rd reuse		6th reuse	
GLF	143 ± 2	137 ± 4	(− 4 %)	136 ± 6	(− 5 %)
DISSCAP	133 ± 18	140 ± 13	(+ 5 %)	141 ± 14	(+ 6 %)
TECNO	133 ± 20	134 ± 16	(+ 1 %)	122 ± 16	(− 8 %)
ASAHI	177 ± 12	104 ± 13 *	(−12 %)	91 + 12 **	(−28 %)

* $p < 0.05$ versus first use
** $p < 0.01$ versus first use

TABLE VIII

Ultrafiltration capacity
ml/mm Hg, hr.

	1st use	3rd reuse	6th reuse
GLF	7.08 ± 1.12	7.01 ± 1.36	7.68 ± 1.81
DISSCAP	7.11 ± 1.23	6.43 ± 1.18 *	7.73 ± 1.78
TECNO	7.78 ± 2.13	9.29 ± 2.89	7.38 ± 2.86
ASAHI	60.88 ± 22.80	37.9 ± 18.32 **	24.64 ± 17.07 **

* $p < 0.05$ versus first use
** $p < 0.01$ versus first use

apparently the Asahi 150 filter is less suited for reprocessing. This does not eliminate the possibility that other capillary dialyzers of a similar or slightly different chemical structure might behave differently.

Conclusion

Hemodiafiltration offers a valuable alternative to conventional dialysis in the case of clinical and/or allergic intolerance towards conventional dialysis, treatment resistent hypertension, and any situation where an inadequate solute elimination is suspected. So far higher cost price seems to inhibit the routine use of hemodiafiltration in all dialysis patients.

References

1. Henderson, L. W.; Livoti, L. G.; Ford, C. A.; Kelly, A. B. and Lysaght, M. J.: Clinical experience with intermittent hemodiafiltration. Trans. Am Soc. Artif. Intern. Organs, 19, 119, 1973.
2. Leber, H. W.; Wizemann, V.; Goubeaud, G.; Rawer, P. and Schuetterle, G.: Simultaneous hemofiltration /hemodialysis: an effective alternative to hemofiltration and conventional hemodialysis in the treatment of uremic patients. Clin. Nephrol., 9, 115, 1978.
3. Vanholder, R.; Verbanck, J.; Schelstraete, J.; de Smet, R. and Ringoir, S.: Unipuncture simultaneous hemofiltration and dialysis. In: Hemodiafiltration. Proceedings 1st. Symposium Giessen 1981. Ed. Schuetterle, G.; Wizemann, V. and Seyffart, G. Oberursel, Verlag Hygieneplan, p. 76, 1982.
4. Sprenger, K. B. G.: Review article: Haemodiafiltration. Life Support Systems, 1, 127, 1983.
5. Hakim, R. M.; Fearon, D. T. and Lazarus, J. M.: Biocompatibility of dialysis membranes: effects of chronic complement activation. Kidney Int., 26, 194, 1984.
6. Vanholder, R.; Piron, M. and Ringoir, S.: Absence of a beneficial haemodynamic effect of bicarbonate versus acetate haemodialysis. Proc. EDTA-ERA, 21, 195, 1984.
7. Lowrie, E. G. and Sargent, J. A.: Clinical example of pharmacokinetic and metabolic modeling: Quantitative and individualized prescription of dialysis therapy. Kidney Int., 18, suppl. 10, 911, 1980.
8. Lowrie, E. G.; Laird, N. M.; Parker, T. F. and Sargent, J. A.: Effect of the hemodialysis prescription on patient morbidity. Report from the National Cooperative Dialysis Study. New Engl. J. Med., 305, 1176, 1981.
9. Schoots, A.; Homan, H. R.; Gladdines, M. M.; Cramers, C. A.; de Smet, R. and Ringoir, S.: Screening of UV-absorbing solutes in uremic serum by reversed phase HPLC-Change of blood levels in different therapies. Clin. Chim. Acta, 146, 37, 1985.