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Biofiltration with and without acetate

P. Zucchelli, A. Santoro and M. Spongano
Divisione di Nefrologia e Dialisi-Malpighi. Policlinico S. Orsola-Malpighi. Bologna (Italy).

Introduction

Standard acetate hemodialysis (HD), wich represents the most economical and widespread form of renal replacement therapy, cannot be considered an ideal treatment for end-stage renal failure (ESRF) because of the frequency of cardiovascular instability and the insufficient correction of the patient's metabolic acidosis.

During the last decade the application of convective mass transport by hemofiltration has been proposed to improve intratreatment dialysis morbidity. But standard hemofiltration cannot provide an adequate solute removal in accordance with the guidelines set by The National Cooperative Dialysis Study [1].

Moreover, over the last few years many experimental and clinical works have put forward some standards for an improved dialytic therapy and a shorter treatment time (table I). To fulfill these basic requirements various treatment methods have been set up providing both an adequate removal of toxic substances as well as cardiovascular stability associated with the possibility of shortening treatment time [2-4]. The relative complexity of the proposed techniques, the need of a rather complex monitoring system and the high cost of commercial sterile replacement solutions may however limit their expansion. In addition, a high blood flow rate of over 400 ml/min is a constant feature in these techniques, although it has been hard to obtain such efficient vascular accesses in diabetic and elderly people, the numbers of whom have been increasing in the ESRF population.

Biofiltration

Hemodiafiltration is an extracorporeal process of blood purification wich combines the best of both diffusive and convective solute transport. Biofiltration (BF) [5, 6] represents a technical simplification of hemodiafiltration with lower running costs, which can be used as a routine treatment in any dialysis unit. The latter technique offer many potential benefits compared to HD as regards biocompatibility, clinical tolerance, the correction of the acid-base status and a reduction in treatment time. The dialyzers used in BF are Biospal 3000 S or Filtral 1.2 both using a new polyacrylonitrile membrane with high diffusive and hydraulic permeability and showing a greater biocompatibility according to the results of specific biological tests [7]. The dialysate flow rate was kept at 500-600 ml/min with the following composition (in mEq/l): Na 140, K 1.8, Mg 0.5, Ca 3.6, Cl 108, acetate 37. The glucose concentration was equal to 1 g/l. The blood flow rate was maintained at 300-350 ml/min. The unheated post-dilution substitution fluid, directly reinfused into the venous bubble trap, was made up as follows (in mEq/l): Na 145, Cl 45, KCO_3 100. However, the composition of the substitution fluid can be modified according to the patient's acid-base status.

The BUN clearance during BF at a blood flow rate of 300 ml/min and at 16.6 ml/min rate of substitution fluid, was approximately 200 ml/min. The behaviour of BUN, creatinine and uric acid during a session of HD and BF is depicted in figure 1. It can be seen that after 3 h BF plasma levels of these small molecules were quite similar to the levels obtained after 4 h HD. Beyond 3 h and half, the BF efficiency, in terms of small molecule removal, sloped off, suggesting that protraction would not have been very useful with a view to more purification. Moreover, mathematical analysis and in vivo testing permitted a volume restriction of 3-3.5 liters of substitution fluid to yeld a sufficient correction of the acid-base status and an adequate extracellular inorganic phosphate removal [8] during 3-3.5 hour run of BF.

BF has been studied for more than 2 years on 12 clinically stable chronic dialysis patients [6]. The long-term acid-base status improved markedly as demonstrated by the significant increase in average pretreatment pH and bicarbonate levels (fig. 2). Three of the 12 patients experienced recurrent symptomatic hypotension during many of their previous dialyses. BF was kept constant at 3 times a week, 3 h/session with 3 liters of substitution fluids. Every 2 months a urea kinetic study was carried out according to the method described by Sargent and Gotch [9]. The protein and caloric intakes were determined every month with dietary interviews. The adequacy of the treatment in terms of urea removal was judged by the Kt/V value [1].

Correspondencia: Dr. P. Zucchelli.
Divisione di Nefrologia.
Policlinico S. Orsola-Malpighi.
Bologna (Italia).

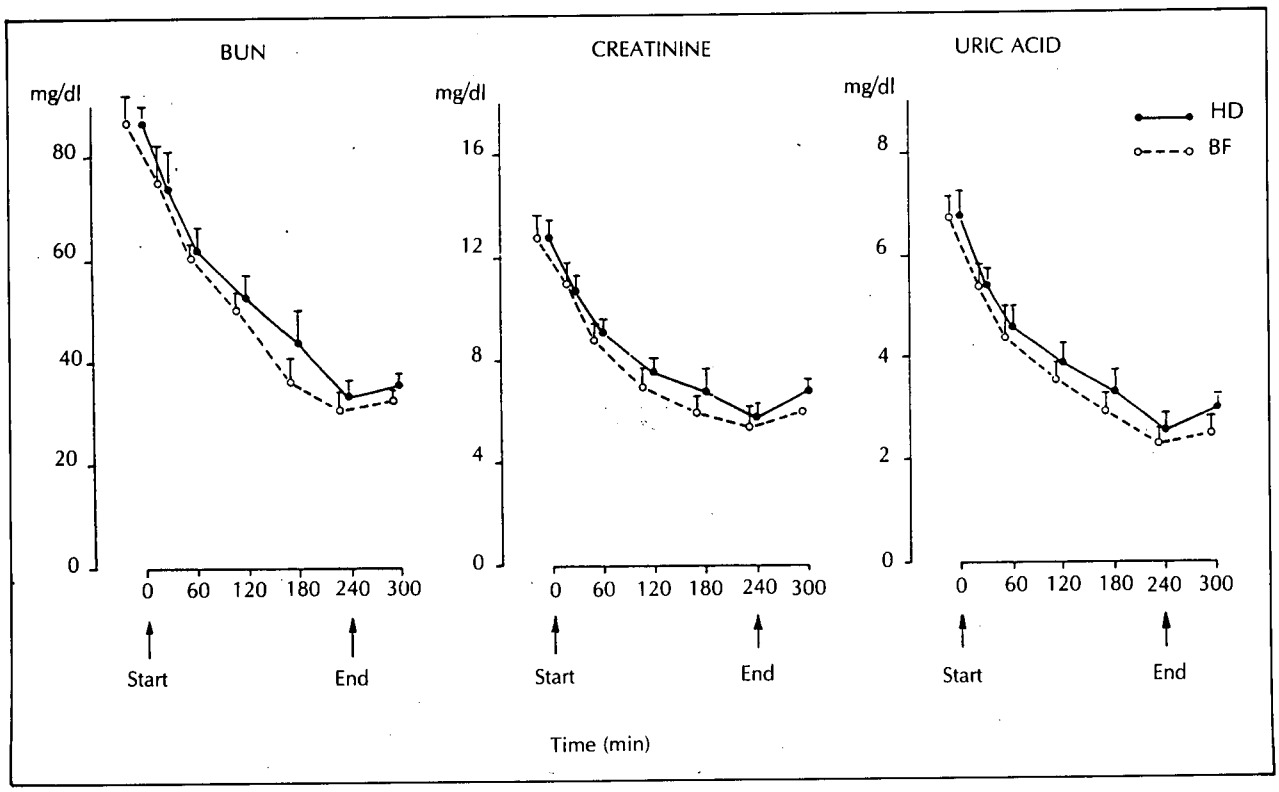

Fig. 1.—BUN, creatinine and uric acid levels during conventional hemodialysis (HD) and biofiltration (BF).

Echocardiographic studies were carried out before BF treatment was begun and every 6 months during its course. All the echocariographic examinations were performed 24 h following the end of the dialysis session [6].

Symptoms of dialysis discomfort were noticeably reduced in BF as opposed to HD and the incidence of hypotensive episodes was significantly fewer in BF as opposed to HD although weight loss was approximately the same (table II). In spite of a shortened treatment time, there was no change in the left ventricular parameters both before and after 2 years of BF in our patients, all of whom had near-normal left ventricular function prior to starting course treatment [6]. BF treatment seemed to induce a moderate but statistically significant increase in dry body weiht and in the protein catabolic rate (PCR). The adequacy of the level of dialysis prescribed is documented by the Kt/V values (table II).

In our opinion, one of the major advantages of BF is the possibility to easily correct the acid-base status despite of the use of acetate dialysate. Moreover, it is possible to modify the Kt/V value, according to the patient's PCR, by changing either the amount of substitution fluid or the blood flow rate and/or the treatment time.

Table I. Proposed present-day guidelines in dialysis

Adequate BUN and middle molecule removal
Adequate dietary protein intake
Biocompatibility of dialytic materials
Correction of uremic acidosis
Satisfactory clinical tolerance
Shortened treatment time

Table II. Comparison between standard hemodialysis (HD) and biofiltration (BF)

	HD	BF
Mean treatment time (min/session)	252 ± 13	194 ± 12
Dry body weight (kg)	64.4 ± 2	65.9 ± 2
PCR (g/kg/day)	1.1 ± 0.08	1.3 ± 0.12
Kt/V urea	1.1 ± 0.04	1.02 ± 0.06
TAC urea (mg/dl)	65.5 ± 2.9	67.6 ± 4.1
Incidence of hypotensive episodes (%) (SBP < 90 mmHg)	20 ± 3	8 ± 5
Incidence of symptomatic hypotension (%)	14 ± 2	5 ± 3
Intradialytic body weight loss (kg).	3 ± 0.5	2.9 ± 0.6

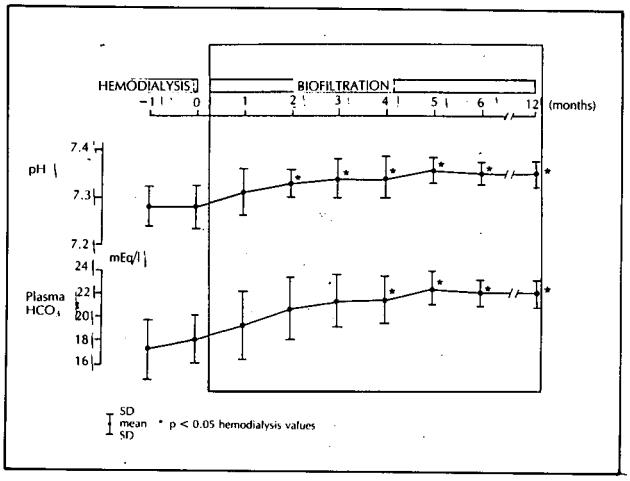

Fig. 2.—Monthly predialysis values of pH and plasma bicarbonate during acetate hemodialysis and biofiltration.

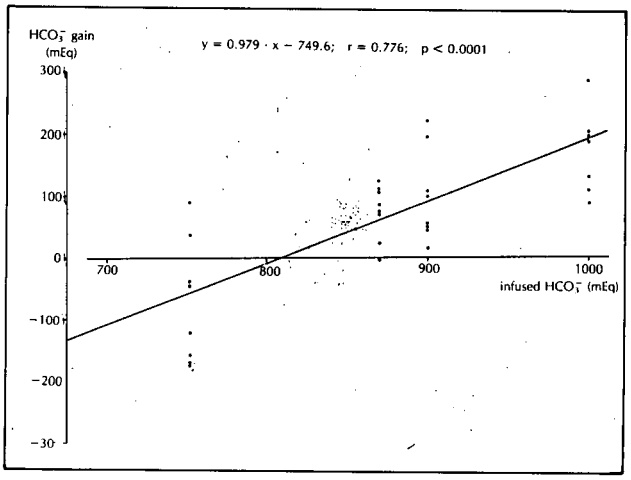

Fig. 3.—Schematic diagram of acetate-free biofiltration circuit.

Acetate-free Biofiltration

Several studies have recently shown the beneficial effects of bicarbonate dialysis in reducing dialysis-associated morbidity in critically ill patients, especially with the use of high-efficiency dialyzers. However, because of the low solubility of sodium bicarbonate and the precipitation of calcium and magnesium carbonate, the bicarbonate-containing dialysate must be prepared sequentially from two separate concentrate solutions. We are now proposing the absence of buffers in the dialysate using the so-called acetate-free biofiltration (AFB), technique in which bicarbonate is not administered in the bath but only in the replacement fluid [10]. This method eliminates the need to have complicated hardware and frequent servicing of the delivery system as happens in standard bicarbonate dialysis.

A) Acute study. Figure 3 is a schematic diagram of the AFB system. A 1.2 m^2 polyacrylonitrile hollow fiber hemodiafilter (Filtral, Hospal) was used. The dialysis unit (monitral BSM2, Hospal) was equipped with an automatic ultrafiltration control system, a volumetric reinfusion pump connected to the blood pump and safety devices which operated in a fail-safe manner. The three pumps (infusion, blood and ultrafiltration pumps) were electrically interconnected and if one failed, then all the others would immediately stop.

The blood flow rate was maintained at 300-500 ml/min and was controlled by bubble time (and on a few occasions with Doppler apparatus). The dialysate composition was kept constant at (in mEq/l): sodium 136, potassium 2, calcium 3.7, magnesium 0.5, chloride 142. The glucose concentration was 1 g/l. The dialysate flow rate was 500-550 ml/min and it was checked with timed dialysate collections. The mean dialysate temperature was 38.1° C. The unheated post-dilution bicarbonate solution was directly reinfused into the venous bubble trap. This solution is commercially available in Italy; however, microbiological and endotoxin investigations on substitution fluid were frequently performed and they were negative in all samples.

In order to choose the most suitable concentration of bicarbonate at postdilution, 8 patients treated by

Table III. Protocol of the study in acetate-free biofiltration

Eight patients (3 F, 5 M). Each patient underwent 4 experimental AFB sessions each with different amounts of infusion solution, infused HCO_3 and different ultrafiltration rates:

	Infused solution l/session	Infused HCO_3 mEq/session	UF ml/min
1)	4.5	751	40.5
2)	6.0	870	48.9
3)	4.5	900	42.0
4)	6.0	1002	49.8

The following parameters were measured at the beginning of each session and after 30, 60, 120, 180 min, in sample of blood and dialysate entering and leaving the dialyzer:

pH, pCO_2, pO_2, HCO_3	Gas-analyzer IL 1302
Total CO_2	Corning 965
BUN, Creatinine, Phosphate, Uric Acid	Autoanalyzer SMAC 14

A complete evaluation of these parameters was made on the whole of dialysate collected in toluene.

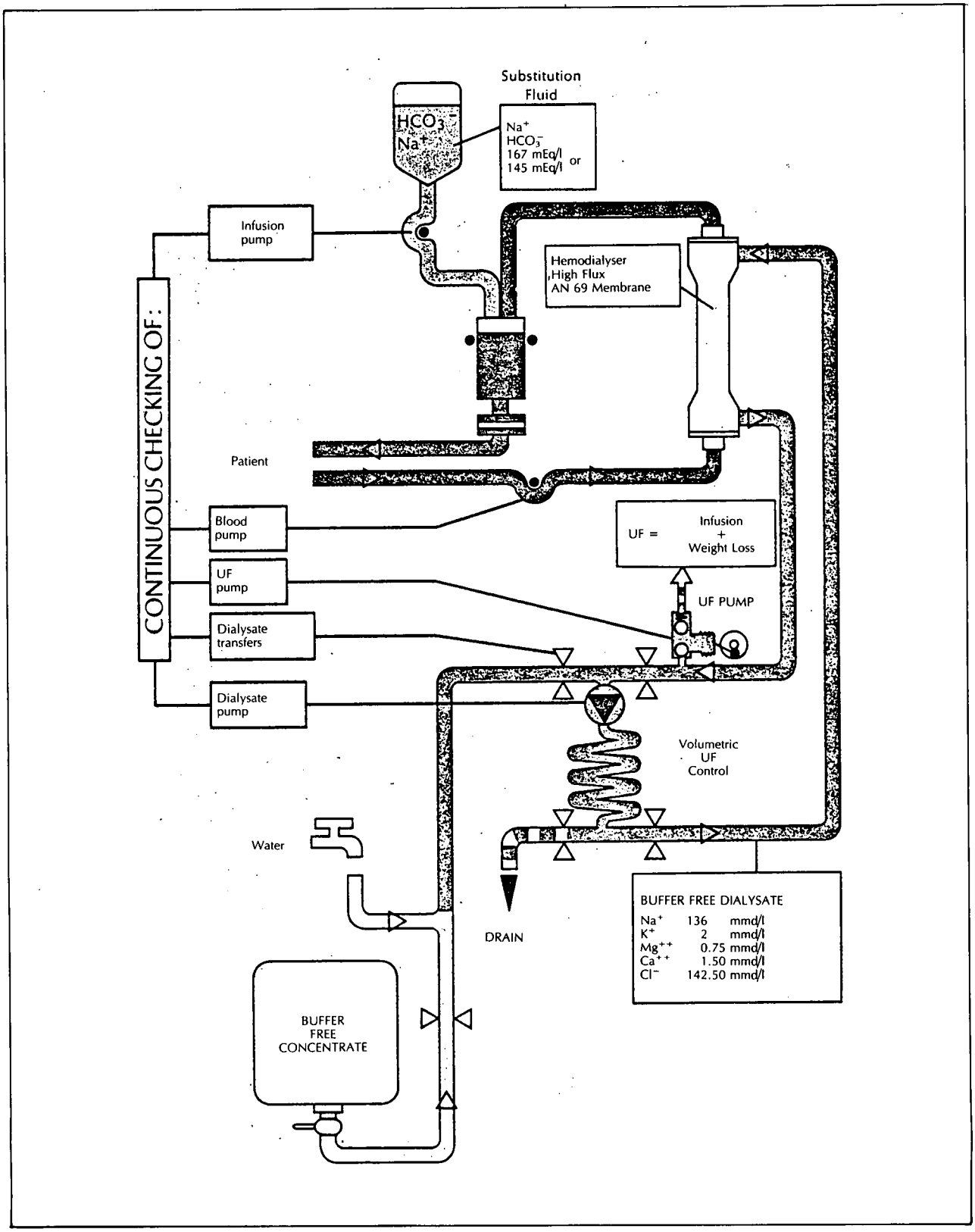

Fig. 4.—Relationship between bicarbonate infused and bicarbonate gain in acetate-free biofiltration.

Table IV. Pre-treatment serum chemistries on standard acetate hemodialysis (HD) and acetate-free biofiltration (AFB)

Parameters	HD	AFB		
		3rd month	6th month	12th month
BUN (mg/dl)	82.0 ± 11.2	79.6 ± 5.9	83.0 ± 6.5	80.2 ± 4.8
Creatinine (mg/dl)	13.3 ± 2.34	12.9 ± 2.7	13.8 ± 2.2	13.0 ± 1.5
Uric acid (mg/dl)	8.4 ± 0.5	7.8 ± 0.6	8.2 ± 0.6	7.8 ± 0.7
Calcium (mg/dl)	9.2 ± 0.25	9.6 ± 0.2	9.3 ± 0.35	9.6 ± 0.3
Phosphate (mg/dl)	4.9 ± 0.41	5.3 ± 0.6	4.5 ± 0.5	4.8 ± 0.5
Sodium (mEq/l)	144.2 ± 2.1	144.0 ± 0.5	145.0 ± 2.7	145.0 ± 1.8
Potassium (mEq/l)	5.5 ± 0.2	5.7 ± 0.4	4.9 ± 0.3	5.3 ± 0.3
Chloride (mEq/l)	104.0 ± 1.3	103.7 ± 2.1	103.2 ± 2.7	103.2 ± 2.0
Hematocrit (%)	25.4 ± 2.1	28.5 ± 0.3	27.6 ± 1.5	27.6 ± 1.7

standard acetate HD underwent 4 experimental AFB sessions each with different amounts of infused HCO_3, as reported in table III. Bicarbonate mass balance analysis demonstrated that it was necessary to administer, in our sample population, more than 800 mEq of HCO_3 during 3 h AFB to obtain a net alkali gain (fig. 4). The average alkali gain was approximately 100 mEq per session with the infusion of 900 mEq in 3 h. The alkali gain was very similar if the AFB was continued up to 4 h with bicarbonate infusion, suggesting that beyond 3 h the efficiency of AFB did not increase in terms of acid-base status. This result can be explained by the existence of an inverse relationship between the bicarbonate loss through the dialysis membrane and the absolute plasma bicarbonate levels. Thus the predialysis HCO_3 level inversely influences the bicarbonate gain. From a practical point of view the system is self-regulating in maintaining the HCO_3 plasma concentration at a fairly stable level by the end of AFB.

B) Long-term study. Four of the 8 dialysis patients who had und ergone the acute experimental study were then treated by chronic AFB therapy, which lasted 3 hours every session for up to 12 months. All the patients had experienced recurrent hypotension during their previous dialyses that consisted of standard acetate hemodialysis, 3 times a week, 4 h/session using a dialyzer with a polyacrylonitrile membrane and a surface area of 1 m^2. AFB was performed with a 1.2 m^2 polyacrylonitrile hemodialyzer (Filtral 1.2, Hospal) at a mean blood flow of 315 ± 11 ml/min and a dialysate flow of 540 ± 12 ml/min. The dialysate composition was the same as in the acute study. On the basis of the calculated losses in acetate dialysis [11] and considering the result of the previous reported acute study, we chose to administer 882-914 mEq of sodium bicarbonate in the substitution fluid during the 3 h session (167 mEq/l for the first 30 to 60 min at 1.8-2 l/h and then 145 mEq/l at 21/h infusion rate). The mean reinfusion flow and ultrafiltration rate were 33.3 ± 0.6 ml/min and 49.5 ± 2.6 ml/min, respectively.

AFB was given long-term testing on these 4 patients. The biochemical profile in long-term AFB was not different from the one assessed in conventional acetate hemodialysis lasting 240-250 min (table IV). The acid-base status (table V) of the 4 patients on chronic AFB showed a stabilization on the pre-treatment bicarbonate concentration at approximately 22 mEq/l after 6 months. AFB provided adequate therapy and increased patient comfort and stability (table VI). In fact, a significant reduction in hypotensive and cramping episodes was recorded despite shorter treatment time. The amount of saline used to counteract hypotension was reduced from approximately 18 liters/year (115.4 ml/session) during standard hemodialysis to only 4 liters/year (25.6 ml/session) during AFB. The incidence of pre-dialysis

Table V. Pre-treatment blood gases and acid-base parameters on standard acetate hemodialysis (HD) and acetate-free biofiltration (AFB)

	HD	AFB		
		3rd month	6th month	12th month
pH	7.309 ± 0.02	7.33 ± 0.04	7.36 ± 0.01	7.38 ± 0.02
pCO_2 (mmHg)	35.02 ± 0.8	38.0 ± 1.7	39.1 ± 0.5	38.8 ± 1.8
TCO_2 (mEq/l)	20.4 ± 1.1	23.5 ± 0.3	22.4 ± 0.4	23.7 ± 0.8
HCO_3 (mEq/l)	18.1 ± 2.2	22.0 ± 0.2	21.2 ± 0.4	22.8 ± 0.4
pO_2 (mmHg)	89.7 ± 2.8	93.5 ± 1.8	95.3 ± 9.0	90.7 ± 2.4

Table VI. Therapy prescription and clinical data during standard acetate hemodialysis and long-term acetate-free biofiltration

	Standard hemodialysis	Acetate-free biofiltration
Duration (min)	248 ± 4.9	194 ± 9.0
Blood flow rate (ml/min)	285 ± 10	315 ± 11
Urea clearance (ml/min)	169 ± 7	208 ± 4.3
Vit B_{12} clearance (ml/min)	46 ± 7	81 ± 3.4
Kt/V	1.1 ± 0.05	1.1 ± 0.07
TAC Urea (mg/dl)	60 ± 3.6	63 ± 8.1
PCR (g/kg/day)	1.10 ± 0.09	1.15 ± 0.10
Dry body weight (kg)	66.9 ± 2.6	67.2 ± 2.0
Interdialytic body weight gain (kg)	2.7 ± 0.3	2.0 ± 0.5
% Hypotensive episodes (SBP < < 90 mmHg)	17.8	3.04
No. days in hospital per patient/ year	10	4

hypertension (blood pressure > 150/90 mmHg) remained very low and unchanged in the long-term study.

Finally, there were no significant changes (only a slight improvement) in the left ventricular parameters studied both before (during acetate hemodialysis) and after 12 months of AFB.

Discussion and Conclusion

Standard Biofiltration can be considered a technical modification of hemodiafiltration with reduction of costs and technical as well as practical simplification. Despite the one hour reduction in treatment time, the BF efficiency in terms of removal of small solutes is in the same range as achieved by conventional hemodialysis. The Kt/V and TACurea values can be easily personalized in BF according to the patient's PCR, and correspond, in our study, to what is recommended by Gotch and Sargent [1]. We observed, with BF, a significant reduction in the incidence of hypotensive episodes as opposed to conventional hemodialysis, with no changes in intersession weight gain and left ventricular function. Moreover the significant improvement of nutritional status in BF can be probably explained by better correction of uremic acidosis.

In conclusion, we think that those patients who frequently experience symptoms related to fluid overload or dialysis discomfort during conventional acetate HD should achieve better results with biofiltration. Therefore, this method constitutes an important, lower-cost alternative to both hemodiafiltration and bicarbonate dialysis, provided that a polyacrylonitrile membrane is used, which is considered high biocompatible [5].

Nevertheless, in patients intolerant to acetate, its continuous use in the dialysate may contribute to cardiovascular instability [12]. In fact, several studies have shown that bicarbonate dialysis offers a variety of benefits both in reducing dialysis morbidity and in improving uremic acidosis [13]. Furthermore, bicarbonate in dialysate is especially indicated when high-efficiency treatments are performed [14].

Taking into account these considerations we have suggested the AFB technique. In AFB, bicarbonate is administered in the replacement solution to avoid some of the disadvantages of bicarbonate dialysis, such as the need for complex high-maintenance hardware, and the risk of microbiological and pyrogen contamination of bicarbonate concentrates [15].

In AFB, the amount of bicarbonate that ought to be administered in the replacement solution is equal to the patient's bicarbonate deficiency plus the bicarbonate lost through the dialyzer. In our sample population, having 3 dialysis sessions/week with a polyacrylonitrile membrane, approximately 900 mEq of bicarbonate per session are needed to offset the interdialytic endogenous acid production and bicarbonate loss through the dialyzer.

In the chronic study with approximately 900 mEq per session, the predialytic bicarbonate levels increased progressively from 18-20 mEq/l to 22-23 mEq/l with no episodes of post-dialitic alkalosis. The absence of bicarbonate in the dialysate accounts for an inverse relationship between plasma bicarbonate and bicarbonate lost through the dialyzer. The system is therefore self-regulating in keeping the end-session plasma bicarbonats at a fairly stable level thus avoiding the risk of metabolic alkalosis. Thus AFB permits an optimum correction of metabolic acidosis, which can be tailored to the patient's bicarbonate needs.

AFB significantly decreases the incidence of hypotension in chronic dialysis patients with recurrent intradialytic hypotensive episodes. A significant reduction in treatment time is also possible with AFB without compromising the adequacy of therapy or patient comfort. Moreover, AFB may achieve very low rates of intradialytic complications and hospitalization as well as maintain the integrity of the cardiovascular system. No pyrogen reaction or other important side-effects were observed. Finally, AFB is less expensive than bicarbonate dialysis thanks to the lower complexity of the hardware and the less frequent servicing needs [16].

In conclusion, acetate-free BF, like standard BF, provides adequate therapy and increases patient comfort and stability with a significant reduction in intratreatment morbidity. Moreover, it may be considered as an attractive alternative to bicarbonate dialysis.

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