Patients with complex arrhythmias during and after haemodialysis suffer from different regimens of potassium removal

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Abstract
Background. Although sudden death is one of the most frequent causes of death in haemodialysis (HD) patients, the problem of cardiac arrhythmias, the major cause of these outcomes, has been little discussed.

Methods. In 30 arrhythmia-prone HD patients, we compared the arrhythmogenic effects of two dialysis techniques differing in dialysate potassium (K) content. Each patient underwent Acetate-Free Biofiltration sessions with constant (2.5 mEq/l) K (AFB) and sessions with decreasing intra-HD K (AFBK), according to a crossover single blind design. Holter ECG recording and plasma electrolyte measurements were performed during each dialysis session.

Results. There was a tendency in the whole sample for arrhythmia appearance in AFBK to be reduced as compared to AFB throughout the 24 hr period, although this reduction was not statistically significant. In the subset of patients sensitive to dialysis as far as arrhythmia onset is concerned, AFBK was systematically less arrhythmogenic than AFB (P < 0.01). The highest difference was achieved around the 14th hour after the end of dialysis, when the premature ventricular contractions in AFB were 3.9 times higher than in AFBK (P < 0.05). Potassium kinetics differed between the two procedures. At the first hour of treatment, the plasma K concentration was lower in AFB than in AFBK (3.67 ± 0.15 mEq/l in AFB vs 4.06 ± 0.13 mEq/l in AFBK, P = 0.05).

Conclusions. Our study shows a greater arrhythmogenic activity with the use of a constant and relatively low K concentration as compared to decreasing K profiling in dialysis-sensitive arrhythmic patients. Smoother K removal may well engender a kind of protective effect.

Keywords: chronic haemodialysis; electrophysiology; electrolytes; heart disease; hypokalemia

Introduction
Despite the substantial progress made in dialysis technology, cardiovascular diseases remain the single most common cause of death in chronic dialysis patients [1]. Nearly half of deaths on maintenance haemodialysis (HD) are attributed to myocardial infarction, cardiac arrest and other cardiac reasons [1,2]. In fact, among chronic dialysis patients, the major prevalence of diabetes, anaemia, hyperparathyroidism and hypertension favours structural heart diseases [3]. Moreover, fluid overload and metabolic abnormalities, such as metabolic acidosis, dyskalemia and dysmagnesemia, lead to an increased risk of clinically significant ventricular arrhythmias and sudden cardiac death [4].

However, relatively few studies have examined patient- and HD-specific factors that might be associated with a higher risk of developing cardiac arrhythmias and, above all, the moment of highest arrhythmia risk during or after the HD session. Hence, we have undertaken this study of arrhythmias in the short term in order to evaluate the role of one of the major factors in the genesis of HD arrhythmias, i.e. potassium (K) changes during dialysis.

We have evaluated the effects of two different regimens of dialysis potassium removal (constant dialysate potassium, AFB, and potassium profiled dialysate, AFBK) in patients with a tendency to develop arrhythmias during HD. Our chief interest was to identify the moment of the greatest susceptibility to cardiac rhythm disorders during the dialysis cycle.

Subjects and methods
End-stage renal disease patients (residual diuresis less than 500 ml/d) were considered eligible for the study if on thrice-weekly standard bicarbonate dialysis for at least 6 months, and if aged between 18 and 80 years.

Patients were included in the study if affected by grade 2 cardiac arrhythmias according to Lown's classification
Fig. 1. Experimental design and scheme of 24 h ECG recording during the patient’s enrolment in conventional dialysis and during the study phase. Experimental design was of the AAB vs BBA (A = AFB and B = AFBK) kind. Each patient was checked for inclusion and exclusion criteria on his/her own usual dialysis therapy and by ECG Holter on the midweek dialysis lasting 24 h. Then he/she was centrally randomised and admitted to the study in one of the two arms. The ECG Holter was replicated in the first and midweek dialysis in the study phase. The same scheme was used for all the other instrumental and laboratory assays (electrolytes, homodynamic parameters).

During dialysis (more than 30 pre-mature ventricular complexes per hour). Patients were evaluated for cardiac arrhythmias by 24-h ambulatory ECG Holter during the midweek dialysis.

The following exclusion criteria were also taken into account:

- pacemaker holders,
- anti-hypertensive treatment with beta-blockers or variable doses of digitalis,
- pre-dialysis plasma potassium less than 3 mEq/l,
- poor vascular access requiring single-needle dialysis,
- active malignancy and mental disease.

Study design

This multicentre prospective randomised trial was conducted according to a crossover single-blind (blind to the patient) scheme with two arms (AAB—BBA, Figure 1, where A = Acetate Free Biofiltration, AFB and B = AFBK, Potassium Profiled Acetate Free Biofiltration). As the study period consisted in a change to the usual dialysis therapy, the first period of each arm was replicated to stabilise the patient in the new therapy. Each eligible patient was first studied in his/her usual bicarbonate dialysis, in the midweek dialysis to check compliance with the inclusion and exclusion criteria. Then the patient was randomised to one of the two arms (according to a centralised block balanced scheme stratified per Centre) and was then treated by 2 arms (AAB—BBA, Figure 1, where A = Acetate Free Biofiltration, AFB and B = AFBK, Potassium Profiled Acetate Free Biofiltration). As the study period consisted in a change to the usual dialysis therapy, the first period of each arm was replicated to stabilise the patient in the new therapy. Each eligible patient was first studied in his/her usual bicarbonate dialysis, in the midweek dialysis to check compliance with the inclusion and exclusion criteria. Then the patient was randomised to one of the two arms (according to a centralised block balanced scheme stratified per Centre) and was then treated by 2 weeks in constant potassium AFB or AFBK. In the first two sessions of the second week, each patient was monitored for 24 h by ECG Holter and for biochemical data. At the end of the second week, each patient was switched to AFBK or to AFB, respectively, for one further week of study (Figure 1). Again, each patient was monitored during the first two dialysis sessions of that week.

Interventions and comparison

AFBK (experimental intervention) was compared to conventional AFB with constant dialysate potassium concentration (control treatment), in order to ascertain the different effects as to the appearance of cardiac arrhythmias.

AFB is a diffusive-convective dialysis therapy characterised by the total absence of any buffer in the dialysate and with continuous infusion of a sterile solution of sodium bicarbonate at a concentration ranging from 145 to 167 mEq/l in the post-dilution mode. The AFB with an independent potassium profile used in this study represents a further evolution in traditional AFB and exploits a concentrate in a dual-compartment bag to obtain a potassium profile of a pseudo-exponential type. Details on the precise mechanisms of the dialysate potassium profiling system have been described by our group elsewhere [5].

In both modalities, a polyacrylonitrile haemofilter, of the same size as the one used in the enrolment phase (1.6–2.0 m²), was used.

Time of dialysis, blood, dialysate and infusion flow rate as well as dialysate conductivity, were kept equal in both dialysis modalities. The dialysate composition was set equal in both the treatments except for the potassium content. The latter was set constant during conventional AFB treatment (2.5 mEq/l), while it was set exponentially decreasing over time in AFBK, starting from an initial value 0.5 mEq/l lower than the individual patient’s plasma potassium level and ending at a final value of 1.5 mEq/l.

During the treatments, any additional intake of oral or intravenously delivered potassium was avoided.

Home therapies (except those mentioned in the exclusion criteria) were administered on the basis of the clinical investigator’s judgement at the same doses and frequencies as in the period prior to the start of the study and could not be changed during the study phase.

Measurements

Biochemical measurements

The following parameters were evaluated:

- plasma K⁺, pre- and post-dialysis and 60 min after the start of the treatment,
- plasma ionised calcium (Ca²⁺), sodium (Na⁺) and pH, pre- and post-dialysis.

Blood samples at the first hour and at the end of dialysis were drawn using the slow-flow technique to avoid bias in the electrolyte measures due to potential vascular access and cardiopulmonary recirculation (blood flow rate at 50 ml/min for 2 min before sampling).

ECG recording

A 12-lead ECG Holter (H12, Mortara—Europe) was used for all the recordings. On the day of the dialysis undergoing evaluation, the recording began 1 h before the HD start and lasted for 24 h. Patients were invited to keep track of the main events during the 20 h after the end of dialysis (meal, rest, physical activity, medication, etc.), while all the ECG recordings were centrally blinded and independently analysed.
**Statistics**

**Sample size estimation**

The sample size was calculated assuming the count of premature ventricular complex (PVC) as the main response variable and was made on the basis of the results obtained in a previous pilot study [5]. An average difference of 107 premature ventricular complexes was found between AFB and AFBK with a standard deviation of 337 in a non-selected patient sample. Two-tailed paired t-test was used for the computation assuming a significance level (α error) of 0.05, and a power of 0.8. An effect size of 0.5 seemed to be clinically acceptable and statistically reasonable, considering that in the pilot study a value of 0.35 was found [5]. By these assumptions, a total number of 34 patients was selected patient sample. Two-tailed paired t-test was used for the computation assuming a significance level (α error) of 0.05, and a power of 0.8. An effect size of 0.5 seemed to be clinically acceptable and statistically reasonable, considering that in the pilot study a value of 0.35 was found [5]. By these assumptions, a total number of 34 patients was found. The sample size was not corrected for potential drop-outs, owing to the short length of the study.

**Descriptive statistics and analysis**

The descriptive analysis was based on the mean ± standard error of the mean for the continuous normally distributed variables. Inferential statistics included ANOVA for repeated measures and sign-test according to the statistical distribution of the variables.

**Regulatory considerations**

The Ethical Committees of each participating Centre approved the study. All the patients gave their informed consent before entering the study.

**Results**

Thirty-six patients from six dialysis units were admitted to the study according to the inclusion and exclusion criteria. One patient dropped out and five patients whose ECG recording was unreadable were excluded from the analysis. The 30 studied patients (19 males and 11 females) were 75.5 ± 1.6 years old and had been on maintenance dialysis for 63.6 ± 10.6 months.

The primary renal diseases were mainly chronic interstitial nephritis (40%), followed by polycystic kidney disease (16%), diabetic nephropathy (12%), nephrosclerosis (12%), glomerulonephritis (12%) and uncertain aetiology (8%). Most of these patients were also affected by several comorbidities, among which hypertension was the most common (53.6%), followed by arteriosclerosis (53.3%), neuropathy (25%), diabetes (14.3%), previous myocardial infarction (14.3%), hyperparathyroidism (14.3%) and valvular stenosis (10.7%).

Figure 2 shows the potassium kinetics during the AFB and AFBK study sessions expressed as a percentage change of the pre-dialysis plasma level. The potassium time-course during dialysis apparently differed between the two treatments with a sharper fall in potassium during the first hour of dialysis in AFB than in AFBK, followed by a smooth decrease from the first hour to the end of the treatment both in AFBK and AFB. The pre-dialysis potassium values were relatively low (4.7 ± 0.1 mEq/l in AFB and 4.84 ± 3.11 mEq/l in AFBK) as compared to the dialysis population. However, the absolute values at the first hour (3.66 ± 0.08 mEq/l in AFB vs 4.01 ± 0.09 mEq/l in AFBK) as well as at the end of dialysis (3.20 ± 0.05 mEq/l in AFB vs 3.11 ± 0.06 mEq/l in AFBK) did not reach a statistically significant difference.

Dialyses were delivered under the same operating conditions as regards blood, dialysate flow rate and dialysis time so the main parameters of the dialysis sessions were comparable in the two treatments, except for the plasma to dialysate K⁺ concentration gradient (lower in AFBK than in AFB, Table 1).

The absolute values of all the electrolytes measured pre- and post-dialysis were similar in the two dialysis regimens. Plasma sodium rose from 138.8 ± 0.4 mEq/l to 140.7 ± 0.3, as well as for ionised calcium (from 2.21 ± 0.05 mEq/l to 2.58 ± 0.07 mEq/l) and pH (from 7.36 ± 0.001 to 7.45 ± 0.001).

Figure 3 shows the average number of PVC per each hour (isolated beats, as well as pairs and runs) in AFB and AFBK, derived from the 24-h ECG follow-up, reported on a logarithmic scale. As expected, dialysis tends to trigger or increase the number of PVCs as compared to the interdialysis period to a high extent. In fact, a difference of 0.4 in

**Table 1. Main dialysis parameters as delivered (N = 30)**

<table>
<thead>
<tr>
<th></th>
<th>Weight loss rate (l/h)</th>
<th>Conductivity (mS/cm)</th>
<th>Blood flow rate (ml/cm)</th>
<th>Infusion flow rate (l/h)</th>
<th>ΔK⁺ plasma-dialysate (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB</td>
<td>0.7 ± 0.03</td>
<td>14.9 ± 0.06</td>
<td>302 ± 3</td>
<td>2.1 ± 0.03</td>
<td>2.25 ± 0.11</td>
</tr>
<tr>
<td>AFBK</td>
<td>0.7 ± 0.03</td>
<td>14.9 ± 0.06</td>
<td>297 ± 3</td>
<td>2.1 ± 0.03</td>
<td>0.28 ± 0.11</td>
</tr>
<tr>
<td>P</td>
<td>0.92</td>
<td>0.98</td>
<td>0.271</td>
<td>0.97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The last column reports the potassium concentration gradient between plasma and dialysate at the start of dialysis. Data are reported as mean ± SEM.
log scale between dialysis and interdialysis period means a threefold increase in the number of PVCs.

Nevertheless, the absolute PVC value was not high, either in AFB or AFBK. The nadir achieved in AFB at the fifth hour from the start of dialysis was equal to 30 PVC per hour, but with a very high variability among patients (ranging from 0 to 915 PVC). Although a mean frequency of 30 PVC/h had been used as an inclusion criterion (evaluated during a standard treatment), a few patients had lower PVC frequencies during the study sessions.

In AFBK, a lower appearance of PVC as compared to conventional AFB was apparent, even though the difference did not turn out to be statistically significant ($P = 0.63$, sign test). In particular, the PVC occurrence in the inter-dialysis period during AFB treatments seemed to remain relatively high in absolute values (on average 1.2 ± 0.1).

Most of the PVCs were isolated and just a few of them appeared as pairs or run (isolated PVC 98.3%, pairs 1.6% and runs 0.1%). Table 2 shows the number (log-transformed) of isolated PVC, pairs and runs recorded during the first 2 h of the dialysis treatment, during the whole session and during the 20 post dialysis hours in AFB and AFBK. No significant difference was found between the two treatments in either isolated PVC, or pairs or runs.

Complex PVC appeared also during the interdialysis period, exposing risk patients at risk of complex arrhythmias. Again, there was no statistical difference between the two treatments.

**Post-hoc analysis on dialysis-sensitive patients**

A subset of patients showing a tendency to increase the PVC frequency during the dialysis treatment was identified and defined as “dialysis-sensitive” patients. This subgroup was selected by considering the increase of PVC during dialysis with respect to the interdialysis period in the records of the enrolment phase, as suggested by Redaelli et al. [6]. In particular, patients were included in the analysis if:

$$(\text{PVCs/h})_{\text{Interdialysis Time}} < 2 \text{ and } (\text{PVCs/h})_{\text{Dialysis Time}} = 4 (\text{PVCs/h})_{\text{Interdialysis Time}}$$

Or

$$(\text{PVCs/h})_{\text{Dialysis Time}} = 2 (\text{PVCs/h})_{\text{Interdialysis Time}}$$

Figure 4 shows the above selection criteria in the whole population. Each point represents the PVC ratio (log scale) between dialysis and interdialysis period for each patient. Patients represented by squares (■) and circles (○) are those who matched the above criteria, while the stars (✳) are those excluded from this subset analysis.

The main characteristics of the 12 selected patients were similar to the whole population (age 72.1 ± 2.5 years, time on dialysis 58.2 ± 12.4 months) except for some comorbidities: diabetes was present in 16.7%, hypertension in 66.7%, left ventricular hypertrophy in 33.3% and previous myocardial infarction in 17%.

The average overall number of PVC (isolated beats, pairs and runs) over 24 h in dialysis-sensitive patients is shown in Figure 5. Dialysis confirms triggering the arrhythmia appearance, achieving the highest value by the end of the treatment or 1 h later (on average 30 PVC in AFB and 18 PVC in AFBK).

Moreover, AFBK turned out to be less arrhythmogenic than AFB, not only during dialysis but also throughout the

**Fig. 3.** Time course of PVC (isolated beats, pairs and runs) in a log scale, during 24 h in the two treatments. No statistical significant differences was achieved by sign test ($P = 0.628$) between the two treatments.

**Table 2.** Number (log-transformed) of isolated PVC, pairs and runs (more than two consecutive PVC) during AFB and AFBK (mean ± SEM) in all patients ($N = 30$)

<table>
<thead>
<tr>
<th></th>
<th>Log$_{10}$ (Isolated PVC+1)</th>
<th>Log$_{10}$ (Pairs PVC+1)</th>
<th>Log$_{10}$ (Runs+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB</td>
<td>1.32 ± 0.11</td>
<td>0.93 ± 0.12</td>
<td>0.77 ± 0.05</td>
</tr>
<tr>
<td>AFBK</td>
<td>1.31 ± 0.11</td>
<td>1.09 ± 0.12</td>
<td>0.91 ± 0.09</td>
</tr>
<tr>
<td>$P$</td>
<td>0.49</td>
<td>0.18</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Fig. 4. Identification of patients sensitive to dialysis. The graph represents the ratio in log scale of PVC per hour during dialysis in respect to interdialysis period. Selected patients (square ■ and circle ○) were those whose ratio was greater than or equal to 4 (0.602 in log scale dotted line) if the PVCs per hour during interdialysis were fewer than 2, else whose ratio was greater than 2 (0.301 in the log scale, dotted line) if the PVCs per hour during interdialysis were greater than 2. Stars (✳) refer to patients poorly sensitive to dialysis which include those with a baseline value high during interdialysis but with PVC per hour not increasing during dialysis (ratio close to zero or less).
24 h, and the difference was systematically in favour of AFBK \((P = 0.002, \text{sign test})\). The highest difference was achieved very late after the end of the treatment (around the 13–14th hour) where the average PVC in AFB was 3.9 times higher than in AFBK \((1.17 \pm 0.25 \text{ in AFB against } 0.54 \pm 0.16 \text{ in AFBK}, P < 0.05, t\text{-test})\).

Table 3 shows the isolated PVC, pairs and runs during and after dialysis in AFB and AFBK. Even in the dialysis-sensitive patients most of the PVC appeared as isolated. The highest difference between the two treatments was achieved during the post dialysis period \((P = 0.05, \text{sign-test})\). Complex PVC (pairs or runs) were not statistically different during either the dialysis session or the post-dialysis period.

Figure 6 reports the potassium kinetics of dialysis-sensitive patients. The average absolute values of potassium at the beginning of dialysis were 4.86 \(\pm\) 0.16 mEq/l in AFB and 4.98 \(\pm\) 0.77 mEq/l in AFBK, while the final values were 3.18 \(\pm\) 0.10 in AFB and 3.04 \(\pm\) 0.10 in AFBK, respectively. At the first hour of the treatment, the plasma potassium concentration was lower in AFB than in AFBK \((3.67 \pm 0.15 \text{ mEq/l in AFB vs } 4.06 \pm 0.13 \text{ mEq/l in AFBK})\). The ANOVA for repeated measures revealed a statistically significant difference in the time-per-dialysis interaction \((P = 0.003)\).

### Discussion

This study confirms that dialysis increases the arrhythmogenic activity with respect to the interdialysis period to a great extent. Moreover, a tendency to reduce the arrhythmia appearance in AFBK compared to AFB throughout the 24 h was observed, although it did not reach statistical significance. The low number of patients with serious arrhythmias during the study sessions, notwithstanding their selection on the grounds of the presence of intradialysis arrhythmias, could be one of the explanations for the lack of evidence for significant differences on the statistical level. In support of this hypothesis, there is the datum obtained in the post-hoc analysis. In the subgroup of patients not only affected by cardiac arrhythmias during dialysis, as specified in the inclusion criteria of the study, but also presenting a consistent increase in arrhythmogenic activity during their dialysis sessions, the incidence of PVCs during and after the treatment is significantly higher in AFB than in AFBK.

The observation that two distinct patterns of arrhythmia appearance can be identified among arrhythmic dialysis patients was first made by Abe et al. [12]. They showed patients having almost constant PCV throughout the 24 h ECG recording and patients with a marked increase during dialysis and the early post-dialysis period. Redaelli et al. [6] only included the dialysis-sensitive patients in their pioneering study on the effect of potassium removal on the control of ventricular arrhythmias. Accordingly, our results confirm that the acute effects of dialysis therapy on the control of cardiac arrhythmias could be significant only in dialysis-sensitive patients. It is worth pointing out that in our population of arrhythmic patients the dialysis-sensitive patients were 40% of the total.

In conventional HD with constant and low potassium (range 0–2.5 mEq/l) a large amount of potassium is abruptly removed from the extracellular space [5,7]. Most of this potassium originates from the cells, crosses the cell membrane and appears as isolated PVC in the extracellular space. When dialysate contains a higher potassium concentration, intracellular potassium is abruptly removed and the cells appear as pairs or runs [5,7]. The potassium concentration in the dialysate is lower in AFB than in AFBK, and this difference is maintained during dialysis, with a consequent difference in the appearance of PVCs.

In our study, the potassium concentration was lower in AFB than in AFBK for the first 2 hours of the treatment, and the difference was systematically in favour of AFBK. Also, the plasma potassium concentration was lower in AFB than in AFBK at the beginning of dialysis and the early post-dialysis period. Redaelli et al. [6]. They showed that the potassium concentration in the dialysate was lower in AFB than in AFBK, and this difference was maintained during dialysis, with a consequent difference in the appearance of PVCs.

### Figure 5

**Analysis of PVC (isolated beats, pairs and runs), expressed in a log scale, in the two treatments on 24 h in 12 selected patients.** Bars below zero represent the difference between the \(\log_{10}\) (PVC + 1) in AFBK minus the \(\log_{10}\) (PVC + 1) in AFB, which resulted to be statistically significant \((\text{sing test}, P = 0.002)\).

### Figure 6

**Plasma potassium concentrations during dialysis in the subset of dialysis-sensitive patients \((N = 12)\), expressed in percentage in respect to the baseline value.** The ANOVA for repeated measures test found out a statistical significant difference in the time-per-treatment interaction \((P = 0.003)\).

### Table 3

<table>
<thead>
<tr>
<th>(N = 12)</th>
<th>Log(_{10}) (Isolated PVC + 1)</th>
<th>Log(_{10}) (Pairs PVC + 1)</th>
<th>Log(_{10}) (Runs + 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB</td>
<td>1.13 (\pm) 0.17</td>
<td>1.49 (\pm) 0.20</td>
<td>2.01 (\pm) 0.21</td>
</tr>
<tr>
<td>AFBK</td>
<td>0.95 (\pm) 0.13</td>
<td>1.37 (\pm) 0.13</td>
<td>1.61 (\pm) 0.18</td>
</tr>
<tr>
<td>(P)</td>
<td>0.20</td>
<td>0.51</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**ANOVA for repeated measures test:** 
- \(P = 0.05, \text{sign-test}\) for isolated PVC.
- \(P = 0.003, \text{sign-test}\) for pairs PVC.
- \(P = 0.003, \text{sign-test}\) for runs PVC.
membrane, the extracellular space (the blood) and the dialysis membrane before reaching the dialysate. The depletion of the potassium reserves within the cells may have important repercussions on cardiac electrophysiology. The K concentration gradient across the cell membrane is critical for the repolarisation process, being responsible for both the resting and action potentials. Potassium fluxes during HD have been associated with an increase in QT interval [8,9], an increase in the dispersion of QT [10] and in the inhomogeneous repolarisation revealed by the analysis of the spatial aspects of T-wave complexity [11]. The resulting repolarisation heterogeneity allows for the onset of distinctive re-entrant arrhythmias, and hypokalemia may act as a triggering factor in the genesis of premature ventricular depolarisations. The incidence of related ECG abnormalities during HD ranges from 18 to 76%, depending on the definition of the abnormal ventricular electrical activity [12]. The development of frequent and complex ventricular arrhythmias has been described pre-eminently during HD sessions against a potassium bath concentration of 2.0 mEq/l, used for an effective removal of potassium during HD [13]. An Italian study by Redaelli et al. [6] has demonstrated a 36% reduction in premature ventricular complexes using a profiling of potassium dialysate concentration in arrhythmic HD patients. Morrison et al. [13] demonstrated decreased ventricular ectopic activity in four out of six patients whose dialysate potassium concentration had changed from 2 to 3.5 mEq/l. In our study, the serum potassium trends are significantly different with the use of constant K concentration (2 mEq/l) in comparison with decreasing K dialysate concentration. The constant K greatly contrasts with the smooth continuous clearance provided by K profiling [5]. In AFBK the profile can be set up in such a way as to remove a quantity of potassium equivalent to a traditional dialysis with constant potassium with the advantage of exploiting the whole duration of the dialysis for its removal through a gradient blood-dialysate constant in time [5,14] and thus have less sudden reductions in the serum potassium in the first part of the dialysis.

In this study, faced with this different behaviour of the serum potassium in 12 patients prone to developing ventricular arrhythmias, we observed a substantially different behaviour in the PVC. Paradoxically, compared with what we might have expected, the moment of major difference in PVC does not come during the dialysis session, but 14 h after the end of dialysis session. It is the first time that this has been highlighted, since most of the studies concerning the relation between potassium removal and arrhythmias have been limited to analysing the variations in the heart rhythm either only during the dialysis session or immediately afterwards [6,12,13]. The study by Redaelli [6] only evaluated the differences in the arrhythmias in the 4 h after the end of the session and the analysis was not prolonged further. Instead, in our study we extended the observation for the whole interdialysis period and found that the major differences occur much later in relation to the end of dialysis.

In the interpretation of this result, however, at least two points need to be clarified: the first is to account for why the differences concerning the onset of PVC between HD with constant K and profiling K appear much later than the end of dialysis session. The second is a clinical point and regards the clinical significance of this increased sensitivity to premature ventricular contraction: it might be prodromic to sustained ventricular arrhythmias and to sudden death so frequently described as the cause of death in dialysis patients.

As concerns the first question on the tendency of dialysis with constant and low K to determine PVC with greater frequency, it can be hypothesised that the dialysis-related disequilibrium between intra- and extra-cellular potassium is not rapidly offset at the end of the dialysis session, but continues for a large portion of the interdialysis period. The duration of a state of electrical susceptibility provoked by dialysis is unpredictable. The demonstration that the post-dialysis rebound of potassium is ten times higher than that of urea and lasts over several hours suggests that the potassium transfer from the cells continues after the end of dialysis [15]. Rombolà et al. [16] found a greater fall in intra-erythrocyte potassium concentration in patients with an arrhythmic tendency, as compared to those without such a tendency. There is evidence that temporal repolarisation instability arises at the level of the single cell, and explanations, such as altered repolarisation currents, abnormal intracellular ionic cycling and disease-induced changes in intercellular coupling, have been proposed [17,18]. In the interdialysis interval, the return of a series of factors destabilising the myocardium, such as fluid overload, increase in blood pressure and the changes in pH and bicarbonates, may act as stressors, conditioning the appearance of ventricular arrhythmias [18,19]. Obviously this may be particularly true for patients with cardiomyopathy, left-ventricular hypertrophy, coronary artery disease and cardiac heart failure, which provide the perfect backdrop for arrhythmias to occur [3,20].

As regards the second question, i.e. the danger or harmlessness of the PVC that appears in the post-dialysis period and its possible connections with sudden death, we can put forward some hypotheses. If we look at matters from the epidemiological point of view, the occurrence of sudden death has been reported as a bimodal, with a 1.7-fold first increased death risk occurring in the 12-h period starting with the dialysis procedure [4]. The second peak of frequency has been described in the 12 h before HD at the end of the weekend interval. Recently, Bleyer et al. [4] examining 80 dialysis patients who met the criteria for sudden death, identified the HD procedure as a major stressor leading to increased sudden death frequency in the 14-h period starting with the dialysis session. In the same study, the author noted that patients who died in the first 12 h interval had a lower serum potassium level in the prior monthly labs. Karnik et al. [17] in another study found that treatment with 0 mEq/l potassium dialysate was associated with an increased risk of death.

In this study we observed that the difference in the terms of PVC between constant K dialysate and K profiling dialysate is more evident in the 14 h following the dialysis procedure. There is a suggestive coincidence between our results and what has been reported with the peak of the greatest frequency of sudden death. Naturally, these are only theoretical speculations that should be corroborated by a larger study, designed differently, which should
demonstrate a higher incidence of sudden death in a group of patients treated by HD with constant 2 mEq/l potassium dialysate in comparison with another group treated with K-profiling dialysis.

In conclusion, the results of the post-hoc analysis of this study suggest that in dialysis-sensitive patients, manipulations in dialysate potassium content not only modify the serum potassium trends, but are also associated with a different appearance of ventricular arrhythmias both during HD and in the inter-dialysis period. However, as this result was only obtained with the post-hoc analysis, a new study is needed to test the hypothesis that AFBK may prevent arrhythmias starting and growing worse during dialysis.

Furthermore, it is likely that the potassium balance alone will not suffice to avert malignant arrhythmias in a patient with structural heart disease, something that usually increases the risk of triggering fatal arrhythmia. A recent investigation documents a protective effect of prophylactic defibrillator implantation in patients with NYHA Class II-CHF [21]. The combination of implantable defibrillator and dynamic adjustments in dialysis bath potassium could be a successful strategy in the prevention of death in patients with cardiac diseases, who show a marked tendency to increase their arrhythmogenic activity both during and after dialysis sessions.

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