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Association of serum electrolyte changes during haemodialysis with stimulation of premature ventricular contractions

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Abstract

Background Patients on haemodialysis are predisposed to heart rhythm disorders, including bradyarrhythmia, atrial fibrillation (AF)/atrial flutter, supraventricular/ventricular arrhythmias and sudden cardiac death (SCD) (Turakhia et al. in *Eur Heart J* 39:2314–2325, 2018). In addition to the fact that patients on haemodialysis have a high prevalence of underlying cardiac disease, the stress of haemodialysis itself might also contribute to increased rates of arrhythmias and SCD (Samanta et al. in *Can J Cardiol* 35:1228–1240, 2019).

Methods A Holter 24-h electrocardiogram was set up immediately before the start of haemodialysis for 72 haemodialysis patients (dialysis vintage: 6–8734 days) to record premature ventricular contractions (PVCs) as a marker of arrhythmogenesis for 24 h. Blood samples were also collected every hour during haemodialysis treatment. Each patient was dialyzed against a dialysate consisting of Na⁺ 140 mEq/L, K⁺ 2.0 mEq/L, Ca⁺ 3.0 mEq/L, Mg²⁺ 1.0 mEq/L, Cl⁻ 110 mEq/L, CH₃COO⁻ 8 mmol/L and HCO₃⁻ 30 mEq/L.

Results The frequency of PVCs significantly increased in the 4th (80 ± 34 beats/hour, mean ± S.E.), 5th (79 ± 31 beats/hour) and 6th (105 ± 36 beats/hour) hours ($F = 5.24$, $p < 0.00001$, $n = 72$). The lowest left ventricular ejection fraction (LVEF, $p = 0.001$) and the highest b-type natriuretic peptide (BNP) levels ($p = 0.049$) were found in patients with the highest PVC counts. There was an association of positive changes in both serum K⁺ ($\beta \pm$ S.E., 9.7 ± 2.4 , $p = 0.0002$), Mg²⁺ (43.2 ± 10.3 , $p = 0.0001$) and HCO₃⁻ (5.3 ± 1.8 , $p = 0.005$) with the frequency of PVCs for 4 h immediately after dialysis. During the same period, there was an association of lower serum K⁺ (-8.37 ± 2.16 , $p = 0.0003$) and higher Ca²⁺ (73.4 ± 18.0 , $p = 0.0002$) with the frequency of PVCs.

Conclusions Haemodialysis stimulated PVC generation, and this effect was especially prominent during the period immediately after haemodialysis. Some serum electrolyte changes affected this PVC stimulation. A positive change in serum K⁺ or Mg²⁺ and a negative change in serum Ca²⁺ during dialysis are risk factors for stimulating PVCs, particularly in patients with lower serum K⁺ or higher serum Ca²⁺ levels at the start of dialysis.

Keywords Haemodialysis, Premature ventricular contraction, Potassium, Calcium, Magnesium, Holter electrocardiogram

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Background

Patients on haemodialysis are predisposed to heart rhythm disorders, bradyarrhythmia, atrial fibrillation (AF)/atrial flutter, supraventricular/ventricular arrhythmias and sudden cardiac death (SCD) [1]. In addition to



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the fact that patients on haemodialysis have a high prevalence of underlying cardiac disease, the stress of haemodialysis itself might also contribute to increased rates of arrhythmias and SCD [2].

In fact, haemodialysis is associated with rapid fluid and electrolyte shifts. A number of cohort studies suggested that arrhythmias are dependent not only on low dialysate K⁺ concentrations but also on the slope of K⁺ changes during haemodialysis sessions, although this slope was not directly observed in any of the studies [3–6]. K⁺ may not be the only electrolyte with concentration changes during haemodialysis that would cause arrhythmias and SCD, either [7].

Among arrhythmias, our preliminary observation as well as the previous report showed that haemodialysis directly triggered or increased number of PVCs as compared to the interdialysis period [6, 8]. VPCs may trigger fatal cardiac arrhythmias in patients with underlining heart disease [9, 10]. Both supraventricular premature contractions (SVPCs) or bradyarrhythmia increased during interdialysis period before next haemodialysis session [6]. Thus, we hypothesized that haemodialysis directly stimulates generation of PVCs in certain condition of patients and/or dialysis prescription. In order to answer

this hypothesis, we investigated an association of intradialytic changes in serum electrolytes (slope) as well as haemodynamic parameters during haemodialysis with the increment of PVCs by using 24-h electrocardiogram monitoring.

Methods

Study population

Five hundred and sixty-seven patients underwent maintenance haemodialysis between April 2017 and December 2018 in our hospital. Four hundred and fifty patients were eligible for the study after the exclusion of patients with continuous atrial fibrillation, those equipped with a permanent pacemaker, those taking any medication with the risk of prolonging the QT interval and those taking antiarrhythmic drugs other than beta blockers (Fig. 1). Among the eligible patients, seventy-two patients agreed to participate in this study and underwent Holter electrocardiography. Finally, a complete set of data was obtained for 52 patients for analysis. The duration of haemodialysis therapy ranged from 6 to 8734 days, and the age of the patients ranged from 46 to 87 (69.7 ± 9.4) years. The aetiologies of chronic kidney disease (CKD) were diabetic kidney disease (N=32),

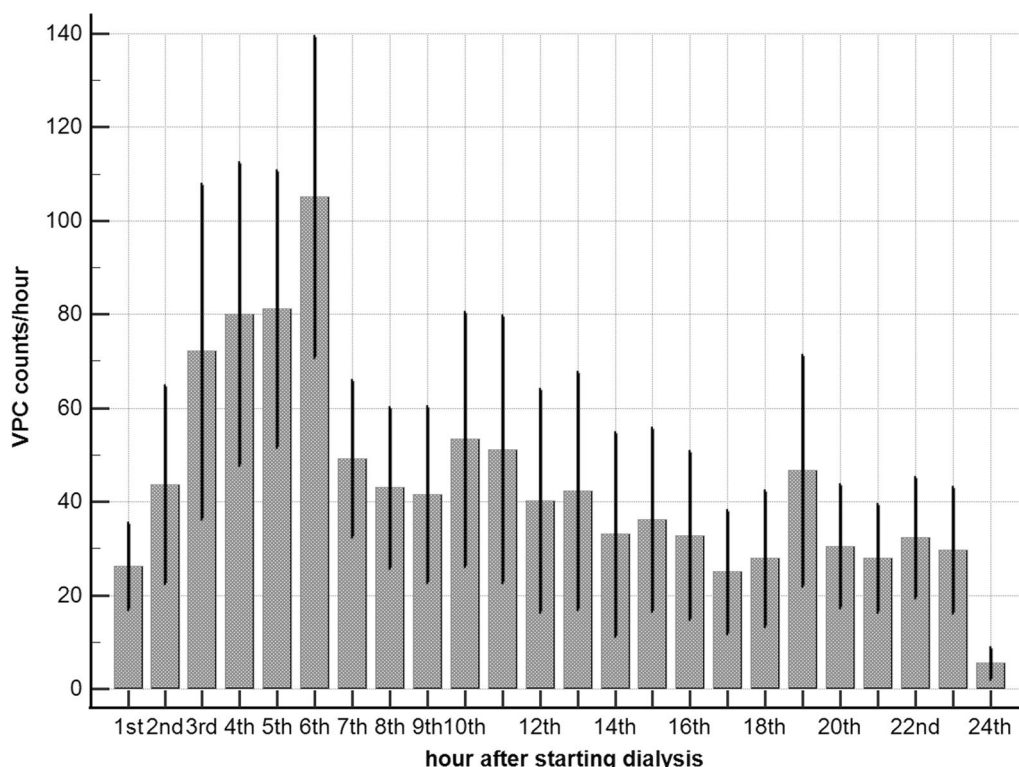


Fig. 1 Change in PVC frequency after the beginning of dialysis. Each column represents mean value of PVC counts in an hour, and each bar represents a standard error of mean. *PVC* premature ventricular contraction

hypertensive nephrosclerosis ($N=14$), glomerulonephritis ($N=4$) and unknown ($N=2$). The type of vascular access was arteriovenous (AV) fistula ($N=36$), AV graft ($N=6$), catheter ($N=5$) and subcutaneously fixed superficial artery ($N=5$). Fourteen patients had a previous history of ischaemic heart disease. Two patients showed an apparent valvular heart disease. Ten patients were prescribed β -blockers. The antihypertensive drugs used were calcium antagonists ($N=26$), angiotensin receptor antagonists ($N=23$) and α -blockers ($N=6$). Thirty-nine patients were given erythropoiesis-stimulating agents.

Informed consent was obtained from all individual participants included in the study. This study was approved by the ethics committee of Itabashi Chuo Medical Hospital and conformed to the Declaration of Helsinki, as revised in 2013 (Approval number: #20161227).

Haemodialysis prescription

Haemodialysis was performed three times a week for 3 h ($N=2$), 3.5 h ($N=1$), or 4 h ($N=49$) per session. The blood flow rate was 150–250 ml/min, and the dialysate flow rate was maintained at 500 ml/min. The mean ultrafiltration rate (UFR) was 2.48 L/session. The dialysate consisted of Na^+ 140 mEq/L, K^+ 2.0 mEq/L, Ca^{2+} 3.0 mEq/L, Mg^{2+} 1.0 mEq/L, Cl^- 110 mEq/L, CH_3COO^- 8 mmol/L and HCO_3^- 30 mEq/L.

Protocol

Holter 24-h ECG (RAC-3103, Nihon Kohden Co., Tokyo) was set up by an electrocardiogram (ECG) laboratory technician before the start of haemodialysis (first session of the week), and the frequencies of arrhythmia and the QT interval were continuously recorded for 24 h. Measurements were obtained from three consecutive complexes in each lead, and the mean value was used, according to the literature [11]. PVCs were automatically counted, and cardiologists reviewed the precision of the mechanical counts.

Blood samples were withdrawn from the arterial side of the vascular access every hour of haemodialysis treatment, and Na^+ , K^+ , Cl^- , Ca^{2+} and HCO_3^- were measured immediately using a blood gas analyser (RAPID Lab 348EX, Siemens Healthcare Diagnostics Manufacturing Ltd, Tokyo). The Mg^{2+} concentration and other blood biochemical parameters were analysed by an automatic analyser (DxC 700 AU, BECKMAN COULTER, Tokyo).

Statistical analyses

Baseline demographics, dialysis parameters and laboratory characteristics are presented as the mean \pm standard deviation (SD) or standard error (SE) or the median and interquartile range (IQR) for continuous variables;

per cent (n/N) is used for categorical variables. Time-averaged laboratory or prescription values were analysed using the mean or median value of all sessions. The Friedman test for nonparametric data was employed to examine the significance of the time-dependent change in PVC frequency. ANOVA and the Kruskal–Wallis test were used to analyse baseline characteristics and predialysis laboratory data according to quantiles of the observed number of PVC counts during haemodialysis for continuous variables, and the chi-squared test was used for categorical variables. Multiple regression analysis was used to analyse associations of electrolytes and intradialytic changes in fluid or electrolytes with haemodialysis-related PVC. The number of dependent variables in a single model was limited to four or five, and automatic weighted regression was applied to correct for heteroscedasticity. Combinations of the independent variables with a high variance inflation factor ($\text{VIF} > 10$) were excluded from the model to avoid multicollinearity among the independent variables. All analyses were computed using MedCalc® ver. 19.5.1 (MedCalc Software Ltd, Belgium) with $p < 0.05$ considered indicative of significance.

Results

Frequency of PVCs during and after haemodialysis sessions

The frequency of PVCs significantly increased in the 4th (mean \pm S.E., 80 ± 34 beats/hour), 5th (79 ± 31 beats/hour) and 6th (105 ± 36 beats/hour) hours after starting dialysis compared with the starting baseline (22 ± 9 beats/hour) and then stayed continuously low until the 24th hour ($F=5.24$, $p < 0.00001$, $n=72$, Fig. 1). Fifteen patients (20.8%) showed PVCs below 10 count/24 h.

Patient characteristics among tertiles of total 24-h PVC counts

Multiple parameters were compared among the tertiles of total 24-h PVC counts (Table 1). As a result, the youngest age ($p=0.016$), lowest LVEF ($p=0.001$) and highest BNP levels ($p=0.049$) were found in the highest PVC count tertiles.

Effect of serum electrolyte changes and PVC frequency during (period I) or immediately after (period II) haemodialysis

To examine which serum electrolyte change during dialysis stimulates PVCs, multiple regression analysis was used to assess the association between intradialytic changes in serum K^+ , Ca^{2+} , Mg^{2+} and HCO_3^- as independent variables and the percent increase in PVC frequency every 4 h as a dependent variable (Table 2).

Table 1 Comparisons of patient characteristics among tertiles of total 24-h PVC count

	Low PVC (0.18 < counts/min), n = 17	Middle PVC (0.18–4.8 counts/min), n = 18	High PVC (> 4.8 counts/min), n = 17	P
Age (years)	68.24 ± 10.54	74.61 ± 7.41	65.94 ± 8.59*	0.016
Sex (F:M) (%)	47.1	27.8	11.8	0.08
Dialysis vintage (days)	1800 (310, 2947)	811 (63, 2286)	2509 (731, 3124)	0.09
Diabetes (%)	70.6	61.1	58.8	0.75
BMI	21.5 ± 3.5	20.8 ± 3.1	22.8 ± 4.2	0.29
ACS history (%)	23.5	22.2	41.2	0.39
LAD (mm)	42.1 ± 6.5	43.5 ± 5.10	45.8 ± 7.1	0.27
LVEF (%)	66.0 ± 7.3	67.6 ± 10.1	53.0 ± 14.8*	0.001
IVST	11.0 ± 1.4	10.5 ± 0.9	10.6 ± 1.8	0.27
LVDd	45.9 ± 4.2	49.5 ± 6.0	51.1 ± 7.7	0.07
Basal QTc (msec)	413 (402, 437)	429 (381, 450)	411 (397, 423)	0.36
BUN (mg/dL)	50.0 ± 18.0	50.9 ± 17.2	49.9 ± 15.8	0.98
Predialysis sHCO ₃ ⁻ (mEq/L)	21.4 ± 2.7	21.4 ± 3.2	22.1 ± 2.4	0.70
Dialysis change in sHCO ₃ ⁻ (mEq/L)	4.2 ± 2.5	4.0 ± 1.9	3.4 ± 1.9	0.64
Predialysis sNa ⁺ (mEq/L)	134.2 ± 3.9	132.9 ± 4.4	133.1 ± 5.0	0.64
Dialysis change in sNa ⁺ (mEq/L)	0.3 ± 2.2	-0.02 ± 2.6	2.1 ± 3.5*	0.045
Predialysis sK ⁺ (mEq/L)	4.43 ± 0.92	4.12 ± 0.74	4.24 ± 0.76	0.51
Dialysis change in sK ⁺ (mEq/L)	-1.14 ± 0.69	-0.96 ± 0.54	-1.05 ± 0.53	0.65
Predialysis sCa ²⁺ (mmol/L)	1.16 ± 0.10	1.13 ± 0.09	1.19 ± 0.09	0.19
Dialysis change in sCa ²⁺ (mmol/L)	0.07 ± 0.07	0.08 ± 0.07	0.08 ± 0.04	0.19
Predialysis sMg ²⁺ (mg/dL)	2.40 (2.30, 2.60)	2.50 (2.25, 2.60)	2.50 (2.40, 2.73)	0.65
Dialysis change in sMg ²⁺ (mg/dL)	-0.30 (-0.53, -0.20)	-0.30 (-0.50, -0.15)	-0.35 (-0.40, -0.25)	0.68
Haemoglobin (g/dL)	10.3 ± 1.3	10.1 ± 1.6	11.0 ± 2.2	0.32
MAP (mmHg)	130 (122, 133)	125 (114, 131)	117 (103, 123)	0.08
UFR (mL/kg/hour)	11.4 ± 5.4	12.6 ± 4.6	9.8 ± 3.6	0.18
BNP (pg/mL)	191.5 (70.5, 377.5)	191.0 (98.8, 390.3)	411.0* (262.5, 1099.8)	0.049
Mean dialysate temperature (°C)	36.2 (36.1, 36.3)	36.2 (36.1, 36.4)	36.2 (36.1, 36.5)	0.71

Each value is presented as the mean ± standard deviation (SD) for parametric data or median with interquartile range for nonparametric continuous variables. Categorical variables are presented as per cent (n/N)

* $p < 0.05$.

This analysis was performed for two separate periods, during the 4 h of dialysis (period I) and the 4 h right after dialysis (period II), because the slope of serum electrolytes changes reciprocally before and after the end of the dialysis session. During period I, none of the independent variables showed a significant association with the per cent increase in the number of PVCs. Then, the correlation became significant during period II (multiple correlation coefficient = 0.914). During period II, the more positive changes there were in both serum K⁺ (9.7 ± 2.4, $p = 0.0002$), Mg²⁺ (43.2 ± 10.3, $p = 0.0001$) and HCO₃⁻ (5.3 ± 1.8, $p = 0.005$) from the start to the end of dialysis, the higher the number of resulting PVCs. There was also a weak correlation between a negative Ca²⁺ change in model 1 (-60.3 ± 28.6, $p = 0.04$) or in model 3 (-83.9 ± 32.5, $p = 0.013$) and an increase in the number of PVCs.

Effect of predialysis serum electrolyte levels and PVC frequency during (period I) or immediately after (period II) haemodialysis

To examine how serum electrolyte levels at the start of dialysis affect the generation of PVCs, multiple regression analysis was performed to analyse the association between predialysis serum K⁺, Ca²⁺, Mg²⁺ and HCO₃⁻ levels as independent variables and the per cent increase in PVC frequency as a dependent variable (Table 3). This analysis was also conducted for two separate periods, during the 4 h of dialysis (period I) and the 4 h right after dialysis (period II). During period I, none of the independent variables showed a significant correlation with per cent increase in the number of PVCs. Then, the correlation became significant during period II (multiple coefficient = 0.911). During period II, the lower the serum K⁺ (-8.37 ± 2.16, $p = 0.0003$) and higher the Ca²⁺ (73.4 ± 18.0, $p = 0.0002$) levels were, the higher the

Table 2 Associations of serum electrolyte change with % increase in PVCs during (period I) and immediately after haemodialysis (period II)

	Correlation coefficient (period I: during the first 4 h of dialysis)			Correlation coefficient (period II: during the 4 h right after dialysis)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
(mean ± SD or median value of change)	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)
Dialysis change in sK ⁺ (− 1.05 ± 0.58 mEq/L)	− 3.4 ± 5.8 (ns)	4.8 ± 6.3 (ns)	− 3.1 ± 4.9 (ns)	9.7 ± 2.4 (0.0002)	10.9 ± 3.5 (0.034)	18.7 ± 5.5 (0.0013)
Dialysis change in sCa ²⁺ (0.08 ± 0.06 mmol/L)	15.6 ± 60.1 (ns)	− 42.1 ± 70.9 (ns)	2.38 ± 59.2 (ns)	− 60.3 ± 28.6 (0.04)	− 17.8 ± 35.1 (ns)	− 83.9 ± 32.5 (0.013)
Dialysis change in sMg ²⁺ (− 0.30 mg/dL (95%CI: 0.40 to − 0.20))	− 15.5 ± 16.1 (ns)	1.09 ± 16.4 (ns)	− 9.2 ± 16.6 (ns)	43.2 ± 10.3 (0.0001)	26.8 ± 11.5 (0.02)	28.9 ± 11.5 (0.016)
Dialysis change in sHCO ₃ [−] (3.9 ± 2.10 mEq/L)	NA	NA	− 2.4 ± 1.3 (ns)	NA	NA	5.3 ± 1.8 (0.005)
Postdialysis BNP	NA	0.007 ± 0.005 (ns)	NA	NA	0.004 ± 0.003 (ns)	NA

A per cent increase in the number of PVCs was defined as the sum of PVCs every 4 h from the start of dialysis divided by the 24-h total. The “dialysis change in electrolyte” is the value at 240 min minus the predialysis value. Model 2 was adjusted by serum BNP level to avoid confounding by volume overload (n = 52). Model 1 = dialysis change in serum K⁺, Ca²⁺ and Mg²⁺; Model 2 = Model 1 + postdialysis BNP level; Model 3 = Model 1 + dialysis change in serum HCO₃[−]. β, correlation coefficient; S.E., standard error, P, p value; ns, not significant; NA, not available; and CI, confidence interval

Table 3 Associations of basal serum electrolyte levels with per cent increase in the number of PVCs during (period I) and immediately after (period II) haemodialysis

	Correlation coefficient (period I: during the first 4 h of dialysis)			Correlation coefficient (period II: during the 4 h right after dialysis)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)	β ± S.E. (P)
Predialysis K ⁺	− 5.0 ± 4.2 (ns)	− 5.7 ± 3.65 (ns)	− 2.5 ± 4.8 (ns)	− 8.37 ± 2.16 (0.0003)	6.22 ± 2.81 (0.033)	− 7.85 ± 2.79 (0.0072)
Predialysis Ca ²⁺	− 8.70 ± 34.4 (ns)	− 0.15 ± 36.8 (ns)	− 10.9 ± 34.2 (ns)	73.4 ± 18.0 (0.0002)	56.4 ± 20.5 (0.009)	86.3 ± 17.4 (< 0.0001)
Predialysis Mg ²⁺	11.7 ± 11.5 (ns)	− 0.36 ± 8.94 (ns)	− 9.54 ± 10.9 (ns)	− 16.4 ± 9.1 (ns)	− 16.1 ± 9.4 (ns)	− 15.8 ± 9.30 (ns)
Predialysis HCO ₃ [−]	NA	NA	− 1.41 ± 1.33 (ns)	NA	NA	0.16 ± 1.36 (ns)
Post dialysis BNP	NA	0.005 ± 0.005 (ns)	NA	NA	0.003 ± 0.004 (ns)	NA

A percent increase in the number of PVCs was defined as the sum of PVCs every 4 h from the start of dialysis divided by the 24-h total. Model 2 was adjusted by serum BNP level to avoid confounding by volume overload (n = 52). Model 1 = dialysis change in serum K⁺, Ca²⁺ and Mg²⁺; Model 2 = Model 1 + postdialysis BNP level; Model 3 = Model 1 + dialysis change in serum HCO₃[−]. β, correlation coefficient; S.E., standard error; P, p value; and ns, not significant

frequency of PVCs. These associations remained after adjustment for postdialysis BNP levels.

Risk factors for/predictors of PVCs during or directly after haemodialysis

Since the highest PVC tertiles group showed the lowest ejection fraction measured by UCG (Table 1), multiple regression analysis was performed to examine the correlation between cardiac parameters and percent increase in PVC frequency (Table 4). As a result, a larger LAD (1.19 ± 0.34, p = 0.001) caused more PVCs during period I (multiple coefficient = 0.523),

and a lower IVST (− 1.69 ± 0.78, p = 0.037) or LVEF (− 0.61 ± 0.26, p = 0.023) caused more PVCs during period II (multiple coefficient = 0.646).

Relationship between predialysis serum electrolytes and the degree of change during dialysis

Figure 2 illustrates the regression analysis of the association of predialysis levels of serum K⁺, Ca²⁺ and Mg²⁺ with the degree of postdialysis change in each electrolyte. Every predialysis electrolyte level showed a significant linear correlation with postdialysis changes. The

Table 4 Associations of UCG parameters with percent increase in the number of PVCs during haemodialysis

	Period I (4 h during dialysis)	Period II (4 h immediately after dialysis)
UCG parameters mean ± SD or median value	$\beta \pm \text{S.E. (P)}$	$\beta \pm \text{S.E. (P)}$
IVST 10.7 ± 1.4	-2.60 ± 1.66 (ns)	-1.69 ± 0.78 (0.037)
LVEF 66.0% (95% CI 64.0–70.7)	0.02 ± 0.20 (ns)	-0.61 ± 0.26 (0.023)
LAD 43.0 mm (95% CI 41.4–44.7)	1.19 ± 0.34 (0.001)	-0.61 ± 0.36 (ns)
LVDd 48.8 ± 6.4	-0.26 ± 0.37 (ns)	-0.86 ± 0.53 (ns)

IVST, interventricular septum thickness; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; β , correlation coefficient; S.E., standard error; P, p value; ns, not significant; and CI, confidence interval

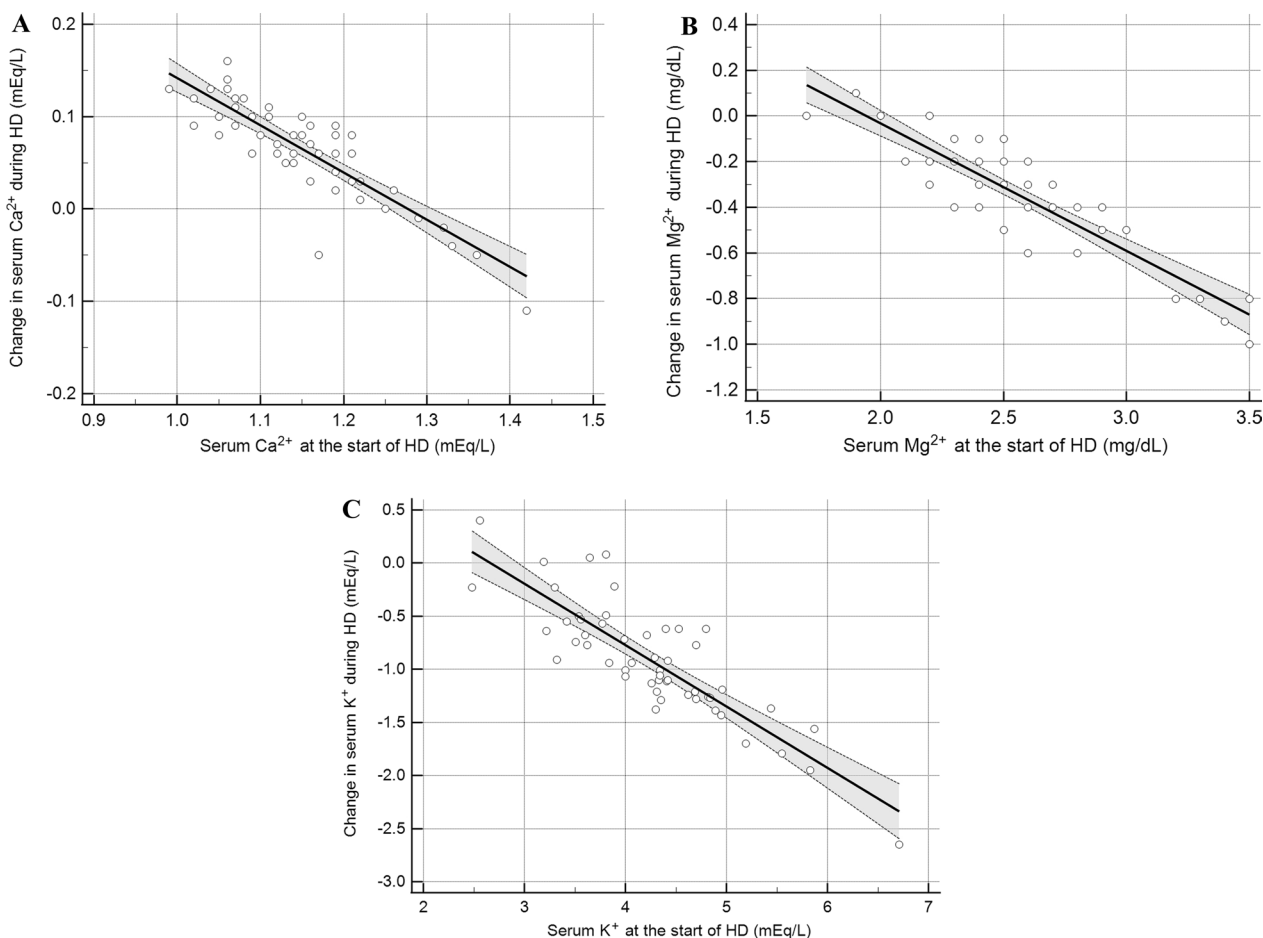


Fig. 2 Relationship between serum electrolyte levels at the beginning of haemodialysis and those during haemodialysis. Each thick straight line represents regression line, and each band represents 95% confidence interval of the regression line. **a** Correlation of predialysis serum Ca^{2+} level and the degree of Ca^{2+} change after 180 min of dialysis against 3.0 mEq/L of dialysate Ca^{2+} . Regression equation; $y = 0.65 - 0.51x$, $r = 0.86$, $p < 0.0001$, $n = 52$. **b** Correlation of predialysis serum Mg^{2+} level and the degree of Mg^{2+} change after 180 min of dialysis against 1.0 mEq/L of dialysate Mg^{2+} . Regression equation; $y = 1.09 - 0.56x$, $r = 0.88$, $p < 0.0001$, $n = 52$. **c** Correlation of predialysis serum K^+ level and the degree of K^+ change after 180 min of dialysis against 2.0 mEq/L of dialysate K^+ . Regression equation; $y = 1.54 - 0.58x$, $R = 0.85$, $p < 0.0001$, $n = 52$, dialysate $\text{K}^+ = 2.0$ mEq/L

serum K^+ level decreased if the predialysis level was above 2.7 mEq/L. The serum Ca^{2+} level increased if the predialysis level was below 1.27 mEq/L and decreased if the predialysis level was above 1.27 mEq/L. The serum Mg^{2+} level decreased if the predialysis level was above 1.95 mg/dL.

Discussion

We studied 72 haemodialysis patients with a Holter electrocardiogram recorder to count PVCs and their association with the dialysis procedure. We found that the PVC frequency reached its peak immediately after the termination of dialysis and continued for 2 h. This was dangerous timing because most of the patients were on their way back home and sudden ambulation may also stimulate a generation of PVCs. A few studies have investigated the frequency of arrhythmias during haemodialysis by using continuous ECG recording. The oldest one was a study of 127 haemodialysis patients in 1988 and demonstrated that the frequency of ventricular arrhythmias rose significantly during the third hour of HD, and this effect lasted for at least 5 h after dialysis [8]. Recently, two studies of 66 and 152 patients showed that tachyarrhythmia increased during 8 h after starting dialysis [12, 13]. Despite the 30-yr progress of haemodialysis therapy, arrhythmogenicity related to the haemodialysis procedure has not been improved.

When we examined the background of patients according to the tertiles of 24-h PVC frequency, patients in the highest PVC tertiles showed the lowest LVEF and the highest serum BNP level. Since a high serum level of BNP usually indicates excess volume gain in haemodialysis patients [14], these results suggest that left heart failure and volume overload are predisposing risk factors for the generation of PVCs immediately after dialysis. However, left heart failure may not be the cause but could be the result of frequent PVCs [15].

To assess which cardiac conditions are vulnerable to PVCs, multiple regression analysis of UCG parameters was performed. As a result, a larger LAD was found to be associated with PVC frequency during dialysis, and a lower LVEF or thinner IVST was associated with PVC frequency during the 4 h immediately after dialysis. These results indicate that dilated cardiomyopathy with volume overload may be the cardiac condition with the highest risk of PVCs.

The most important finding of this study is that an increase in the number of PVCs, particularly immediately after dialysis, was associated with an intradialytic positive K^+ change when patients were dialyzed against 2 mEq/L of K^+ dialysate. In addition, predialysis serum K^+ levels were negatively associated with an increase

in PVC frequency. Since the serum K^+ levels are usually decreased when the predialysis level is over the threshold (2.46 mEq/L) against 2.0 mEq/L of dialysate K^+ (Fig. 2), these 2 sets of results mean that a very low predialysis K^+ level is a high risk factor for generating PVCs. Although none of the studies employed the frequency of PVCs during dialysis as a marker, there have been similar findings for SCD in several cohort studies. These studies reported that a low K^+ dialysate concentration (<2 mEq/L) was associated with a higher incidence of sudden death, especially when predialysis patient serum levels were <5 mEq/L [3–5]. The slope of the decreasing K^+ curve may also be important. One crossover single-blind study compared the effect of different profiles of dialysate K^+ concentrations on the frequency of PVCs and found that a milder K^+ decline curve during the first two hours caused fewer PVCs [6]. This study did not examine the effect of the magnitude of K^+ change during dialysis or the effect of predialysis K^+ levels.

Potassium is not the only electrolyte that shows concentration changes during haemodialysis that would cause arrhythmias and SCD. The serum concentration of magnesium is also recognized in the general population as a risk factor for arrhythmias, but it has been largely ignored in haemodialysis patients. A retrospective cohort study of 142,555 Japanese patients on haemodialysis determined that there was a J-shaped relationship between serum magnesium concentrations and one-year mortality, with a “sweet spot” of approximately 1.2 mmol/L (2.8 mg/dl) [7]. We found that there was a positive association between the Mg^{2+} concentration change and the frequency of PVCs immediately after dialysis. Since the threshold of serum Mg^{2+} , which decreased during dialysis, was 1.95 mg/dL (0.8 mmol/L), most patients showed a decrease in the Mg^{2+} concentration during dialysis. Since no association was found during dialysis, a rebound of serum electrolyte concentration immediately after dialysis sessions could cause PVCs. There was also no association between predialysis Mg^{2+} concentration and PVCs.

Either a higher predialysis Ca^{2+} concentration or a negative change in Ca^{2+} concentration was associated with PVCs immediately after dialysis. Since the threshold of the serum Ca^{2+} change during dialysis was 1.27 mEq/L, serum Ca^{2+} decreased during dialysis if predialysis Ca^{2+} was above 1.27 mEq/L, and the risk of PVCs immediately after dialysis increased.

The weakness of this study was that this was not a controlled study that compared the effect between dialysates with different concentrations of electrolytes. Thus, this study cannot provide evidence that proves the cause-effect relationship. Therefore, this study can provide

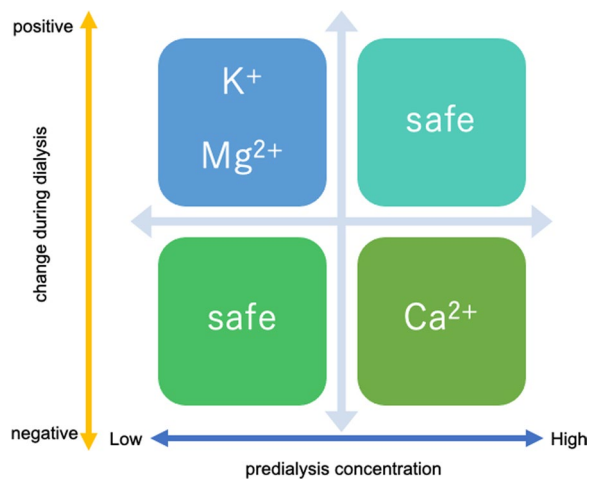


Fig. 3 Conceptual model to illustrate an association of each electrolyte and PVCs

effective data only when dialysates with the same composition are used. Another weakness exists in an uncertainty of PVC frequency as a marker of cardiac outcome in haemodialysis patients, although the significance of VPCs in patients with existing coronary disease as well as in a general population is relatively well understood [9, 10].

The advantage of this study is that this is the first report to successfully show a direct association of the predialysis level of electrolytes and the generation of PVCs. This study suggests that low predialysis K^+ and Mg^{2+} and high Ca^{2+} may be corrected and prevent volume overload, especially for patients with dilated cardiomyopathy, to prevent PVCs.

In summary, Fig. 3 illustrates the associations between electrolyte changes during dialysis and increasing PVC frequency. Every significant association was found only between increases in the number of PVCs immediately after dialysis and positive K^+ or Mg^{2+} change or negative Ca^{2+} change during dialysis. Since these associations were significant for 4 h immediately after dialysis, rebound of these electrolyte concentrations could be a risk factor for generating PVCs in patients with lower predialysis K^+ (and Mg^{2+}) and Ca^{2+} levels when dialyzed against dialysate consisting of Na^+ 140 mEq/L, K^+ 2.0 mEq/L, Ca^{2+} 3.0 mEq/L, Mg^{2+} 1.0 mEq/L, Cl^- 110 mEq/L, CH_3COO^- 8 mmol/L and HCO_3^- 30 mEq/L.

Abbreviations

AF	Atrial fibrillation
AV	Arteriovenous
BNP	B-type natriuretic peptide
CI	Confidence interval
CKD	Chronic kidney disease
ECG	Electrocardiogram

IVST	Interventricular septum thickness
IQR	Interquartile range
LAD	Left atrial dimension
LVDd	Left ventricular end-diastolic dimension
LVEF	Left ventricular ejection fraction
PVCs	Premature ventricular contractions
SD	Standard deviation
SE	Standard error
SCD	Sudden cardiac death
UFR	Ultrafiltration rate
VIF	Variance inflation factor

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Author contributions

EA and YT were involved in the study design and data analysis and wrote the manuscript. YS collected the blood samples and prepared the dialysis prescription for this study. All other authors were also involved in data collection and analysis of Holter ECG. All authors critically revised the report, commented on drafts on the manuscript, approved the manuscript to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All author read and approved the final manuscript.

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Availability of data and materials

The data used in this article are available from the corresponding author.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institution or practice at which the studies were conducted (IRB approval number: 20161227). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Turakhia MP, Blankestijn PJ, Carrero JJ, Clase CM, Deo R, Herzog CA, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J*. 2018;39:2314–25.
- Samanta R, Chan C, Chauhan VS. Arrhythmias and sudden cardiac death in end stage renal disease: epidemiology, risk factors, and management. *Can J Cardiol*. 2019;35:1228–40.
- Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int*. 2011;79:218–27.
- Karnik JA, Young BS, Lew NL, Herget M, Dubinsky C, Lazarus JM, et al. Cardiac arrest and sudden death in dialysis units. *Kidney Int*. 2001;60:350–7.
- Jadoul M, Thumma J, Fuller DS, Tentori F, Li Y, Morgenstern H, et al. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol*. 2012;7:765–74.

6. Santoro A, Mancini E, London G, Mercadal L, Fessy H, Perrone B, et al. Patients with complex arrhythmias during and after haemodialysis suffer from different regimens of potassium removal. *Nephrol Dial Transplant*. 2008;23:1415–21.
7. Sakaguchi Y, Fujii N, Shoji T, Hayashi T, Rakugi H, Isaka Y. Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. *Kidney Int*. 2014;85:174–81.
8. Multicentre, cross-sectional study of ventricular arrhythmias in chronically haemodialysed patients. Gruppo Emodialisi e Patologie Cardiovascolari. *Lancet*. 1988;332:305–9. [https://doi.org/10.1016/s0140-6736\(88\)92357-4](https://doi.org/10.1016/s0140-6736(88)92357-4).
9. Ataklte F, Ergou S, Laukkanen J, Kaptoge S. Meta-analysis of ventricular premature complexes and their relation to cardiac mortality in general populations. *Am J Cardiol*. 2013;112:1263–70.
10. Kostis JB, Byington R, Fredman LM, Goldstein S, Furberg C. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. *J Am Coll Cardiol*. 1987;10:231–42.
11. Sporton SC, Taggart P, Sutton PM, Walker JM, Hardman SM. Acute ischaemia: a dynamic influence on QT dispersion. *Lancet*. 1997;349:306–9.
12. Tumlin JA, Roy-Chaudhury P, Koplan BA, Costea AI, Kher V, Williamson D, et al. Relationship between dialytic parameters and reviewer confirmed arrhythmias in hemodialysis patients in the monitoring in dialysis study. *BMC Nephrol*. 2019;20:80.
13. Rantanen JM, Riahi S, Schmidt EB, Johansen MB, Sogaard P, Christensen JH. Arrhythmias in patients on maintenance dialysis: a cross-sectional study. *Am J Kidney Dis*. 2020;75:214–24.
14. Ishigami J, Iimori S, Kuwahara M, Sasaki S, Tsukamoto Y. Diagnostic value of B-type natriuretic peptide for estimating left atrial size and its usefulness for predicting all-cause mortality and cardiovascular events among chronic haemodialysis patients. *Nephrology*. 2014;19:777–83.
15. Cha Y-M, Lee GK, Klarich KW, Grogan M. Premature ventricular contraction-induced cardiomyopathy. *Circ Arrhythmia Electrophysiol*. 2012;5:229–36.

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