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Effect of serum electrolyte and bicarbonate concentration changes during hemodialysis sessions on heart rate variability

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Abstract

Introduction: **Heart rate variability (HRV) is decreased in dialysis patients, and decreased HRV is an independent risk factor for sudden cardiac death. We aimed to determine the effect of sudden changes in serum electrolyte, bicarbonate concentration and blood pressure on HRV during hemodialysis (HD) sessions in chronic HD patients.**

Methods: **The study population included 75 HD patients (mean age 44.5 ± 10.3 years; 53% female, 13% diabetic) and 35 healthy volunteers (mean age 42.44 ± 11.5 years, 62% female). HRV indexes were analyzed from 24-hour ECG recordings. The time-domain HRV indexes (SDNN, SDANN, RMSSD, pNN50 [%] and HRV TAI) were calculated from these recordings. Pre- and post-HD blood samples were drawn from an arterial line to calculate Na^+, K^+, Ca^{2+}, iCa^{2+} and HCO_3^- concentration gradients.**

Results: **All HRV indexes were significantly lower in dialysis patients than in healthy volunteers ($p<0.05$). The detected SDNN and HRV TAI values were lower in diabetic patients than in nondiabetics. While K^+ concentration was decreased, Ca^{2+} and bicarbonate increased significantly during HD.**

Conclusion: **HRV decreased in chronic HD patients. The decrease in HRV in diabetic uremic patients was higher than in uremic patients without diabetes. The change of serum electrolyte and bicarbonate concentrations during HD did not affect HRV.**

Key words: *Dysautonomy, Electrolyte, Heart rate, Hemodialysis*

Introduction

Autonomic dysfunction is common in patients with chronic renal failure (CRF). Uremic toxins have been implicated as toxic to the central and peripheral nervous systems, and related to hypotension, arrhythmia and increased mortality. Autonomic nervous system (ANS) dysfunction (dysautonomy) occurs in about half of all end-stage renal failure patients. It has been shown that cardiovascular dysautonomy is related to dialysis hypotension, chronic hypotension and arrhythmia, and that it may also be related to sudden cardiac death and increased mortality. ANS functions are evaluated by a Valsalva test, measuring blood pressure response to hand grip exercise, deep breathing tests, orthostatic tests and other similar tests. However, the repeatability and sensitivity of these tests are not adequate (1). Recently, heart rate variability (HRV), which is an easy and noninvasive measure, has been used to determine cardiovascular dysautonomy. HRV means the periodic variations in R–R intervals from beat to beat, and it evaluates the sympathovagal balance at the sinoatrial (SA) level. Variation in R–R intervals can be measured by many methods which can be categorized as time-domain measures, frequency-domain measures and nonlinear/complexity-based measures (2, 3). Time-domain analysis measures normal R–R intervals. Various measurements are calculated from these intervals, including standard deviation of all normal R–R intervals during a 24-hour period (SDNN), standard deviation of 5-minute average of normal R–R intervals (SDANN), average of 5-minute SDNN (ASDNN), root-mean square of the difference of successive

R–R intervals (RMSSD) and the number of instances per hour in which 2 consecutive R–R intervals differ by more than 50 milliseconds over 24 hours (pNN50). SDNN and its variables are thought to represent the sympathetic limb of the autonomic nervous system, whereas RMSSD, NN50 and pNN50 represent the parasympathetic limb (4-6). HRV decreases in patients with CRF. Age, diabetes mellitus (DM), anemia, hypertension and coronary artery disease have also been found to be the main parameters which affect HRV in patients with CRF (7).

During the hemodialysis (HD) process, prominent changes occur in serum electrolyte and bicarbonate levels due to electrolyte shift across the dialyzer membrane. Rapid electrolyte changes may have important consequences such as arrhythmia and sudden cardiac death (8-10). The effect of rapid electrolyte and bicarbonate changes on HRV have not been examined in detail. In this study, our aim was to determine the impact of serum electrolyte and bicarbonate concentration changes during hemodialysis on HRV.

Methods

Patients

The study cohort consisted of 75 HD patients and 35 healthy subjects who gave informed consent. Seventy-five HD patients attending the outpatient clinics of participating hospitals were included in the study. Patients were eligible for inclusion in the study if they had been on HD for at least 3 months, were receiving HD 3 times per week and were medically stable. Reasons for exclusion from the study were history of heart failure, coronary artery disease, malignancy, arrhythmia and vitamin B_{12} deficiency.

Hemodialysis

The monitored HD session was performed for 4 hours, and blood flow rate was maintained at 300 ml/min. The dialysate flow rate was kept at 500 ml/min. The dialysate sodium, potassium, calcium and bicarbonate concentrations were 138, 2, 2.5 and 33 mEq/L, respectively. The temperature of the dialysate was kept constant at 37°C.

Determination of HRV

A digital electrocardiogram (ECG) Holter recorder DR 200/E (Northeast Monitoring Inc., US) with 3 electrodes was used to record 3-channel ECGs in all patients and controls. HRV was analyzed from the Holter monitor recordings using commercially available software (Holter LX Analysis software, version 5.3d).The Holter LX Analysis system automatically edits all artifacts and ectopic beats, and obtains a regular signal by linear interpolation of the HR tachogram. It also calculates the recommended time-domain parameters for HRV according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology guidelines (11).

The time-domain parameters used were mean R–R, SDNN, SDANN, RMSSD and pNN50. The values of all time-domain parameters are expressed in milliseconds.

Laboratory measurements

Serum blood urea nitrogen, creatinine, sodium, potassium, ionized and total calcium were measured at the beginning and end of the dialysis session. The study cohort included 75 HD patients (female: 53%; diabetic: 13.3%; mean age 44.5 ± 10.3 years) and 35 healthy controls (female: 62%; mean age 42.4 ± 11.5 years). An ambulatory electrocardiogram was recorded for 24 hours from the beginning of the mid-week HD session. The time-domain HRV indexes SDNN, SDANN, RMSSD, pNN50 and heart rate variability triangular index (HRV TAI) were calculated from these recordings. Pre- and post-HD blood samples were drawn from an arterial line to calculate Na^+, K^+, Ca^{++}, ionized Ca^{++} (iCa^{++}) and HCO_3^- concentration gradients .

In addition to electrolyte and bicarbonate gradients, age, sex, diabetes mellitus, duration of HD, antihypertensive use and ultrafiltration rate were selected as parameters that may relate to HRV. Linear regression models were fitted for each HRV index using covariates with $p<0.10$ in the univariate analysis.

Results

The characteristics of the 70 subjects are summarized in Table I. Additionally, there were 59 anemic patients in the study: 41 of them used recombinant human erythropoietin, and 18 of them used iron. The mean hemoglobin level was 12.0 ± 0.8 g/dL. Table II shows pre- and post-HD electrolyte and bicarbonate concentrations. There were significant differences in the concentrations of K^+, Ca^{++} and HCO_3^- between pre- and post-HD. Figure 1 shows the mean HRV index data in patients and controls. All indexes were significantly lower in patients than in the control group.

While K^+ concentration was decreased (4.94 ± 0.59 vs. 3.3 ± 0.39 mEq/L; $p<0.001$), Ca^{++} (9.14 ± 0.88 vs. 10 ± 1.0 mEq/L; $p<0.001$) and bicarbonate concentrations (21.09 ± 1.8 vs.

TABLE I
PATIENT CHARACTERISTICS

Age, years	44.5 ± 10.3
Sex, female no, (%)	40 (53.3)
Cause of end-stage renal disease	
Hypertension, no. (%)	20 (26.66)
Diabetes mellitus, no. (%)	10 (13.39)
Others, no. (%)	14 (18.66)
Unknown, no. (%)	31 (41.33)
Duration of dialysis, months (range)	48 (24-84)
Use of antihypertensive drug, no. (%)	15 (20)
CCBs, no. (%)	4 (5.3)
ACEI/ARBs, no. (%)	1 (1.3)
β-Blocker, no. (%)	5 (6.7)
α- Blocker, no. (%)	2 (2.7)
CCB + β-blocker, no. (%)	1 (1.3)
ACEI/ARBs + β-blocker, no. (%)	2 (2.7)
BMI (calculated as kg/m^2)	25.3 ± 5.8
Ultrafiltration rate, ml/hour	594.2 ± 202.3

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blockers; BMI = body mass index; CCB = calcium channel blocker.

TABLE II
COMPARISON OF PRE- AND POST-HD ELECTROLYTE AND BICARBONATE CONCENTRATIONS

Electrolyte	Pre-HD	Post-HD	Rates of changes (%)	p Value
Na^+, mmol/L	136.54 ± 2.68	136.2 ± 2.7	0.29	0.341
K^+, mmol/L	4.94 ± 0.59	3.3 ± 0.39	32.65	<0.001
Ca^{++}, mg/dL	9.14 ± 0.88	10 ± 1.0	9.89	<0.001
iCa, mmol/L	0.86 ± 0.18	0.9 ± 0.19	-4.65	0.103
HCO_3^-, mmol/L	21.09 ± 1.8	26.79 ± 1.46	-27	<0.001

HD = hemodialysis; iCa = ionized Ca.

26.79 ± 1.46 mEq/L; p<0.001) increased significantly. Table III shows the correlations between the HRV indexes and electrolyte and bicarbonate concentration gradients. RMSSD and pNN50 (%) a showed correlation with the ΔiCa^{2+} gradient. In linear regression analysis, electrolyte and bicarbonate gradients did not show any relation with HRV indexes. Linear regression models for SDNN, SDANN and HRV TAI were found to be statistically significant. In these models only DM predicted relevant time-domain indexes. Table IV shows the result of linear regression models.

Discussion

The control of the cardiovascular system is achieved partly by ANS. Based on anatomical and functional differences, the autonomic innervation of the cardiovascular system includes 2 separate divisions: the parasympathetic and sympathetic. Baroreceptors, chemoreceptors, atrial and ventricular receptors, changes in the respiratory, vasomotor and thermoregulatory systems, sympathetic and parasympathetic nerves all play a role in the autonomic control of the cardiovascular system. Heart rate, force of heart contraction and blood pressure changes are adjusted according to physiological demands by the sympathetic and parasympathetic systems. ANS functions are evaluated by performing a series of tests including Valsalva tests, measuring blood pressure, response to hand grip exercise, deep breathing tests and orthostatic tests. However, the reproducibility and sensitivity of these tests are not sufficient (1).

Dysautonomy occurs in over 50% of patients on dialysis (12). Uremia is thought to be the major reason for this dysfunction. Parathyroid hormone and uremic toxins may damage central and peripheral nerves (13). However, other problems such as left ventricular hypertrophy, ischemic heart disease,

TABLE III
CORRELATIONS BETWEEN HRV INDEXES AND ELECTROLYTE, BICARBONATE CONCENTRATION GRADIENTS AND CLINICAL FEATURES

Index	Age	HD duration	Rate of UF	Hb	ΔNa^+	ΔK^+	ΔCa^{2+}	ΔiCa^{2+}	ΔHCO_3^-
SDNN, ms	r=0.085 p=0.470	r=0.239 p=0.039	r=0.095 p=0.419	r=0.247 p=0.032	r=-0.087 p=0.456	r=-0.066 p=0.575	r=0.032 p=0.788	r=0.199 p=0.087	r=-0.095 p=0.420
SDANN, ms	r=0.106 p=0.365	r=0.190 p=0.103	r=0.009 p=0.941	r=0.218 p=0.061	r=-0.113 p=0.333	r=-0.008 p=0.949	r=-0.022 p=0.850	r=0.117 p=0.316	r=-0.061 p=0.603
HRV TAI	r=-0.141 p=0.226	r=0.111 p=0.344	r=0.096 p=0.411	r=0.284 p=0.014	r=0.063 p=0.594	r=-0.123 p=0.294	r=-0.006 p=0.959	r=0.069 p=0.557	r=-0.096 p=0.412
RMSSD, ms	r=-0.087 p=0.460	r=0.000 p=0.998	r=0.045 p=0.701	r=0.128 p=0.273	r=-0.002 p=0.990	r=-0.061 p=0.602	r=0.205 p=0.078	r=0.326 p=0.004	r=-0.018 p=0.881
pNN50, %	r=-0.079 p=0.498	r=-0.037 p=0.754	r=0.011 p=0.926	r=0.158 p=0.176	r=0.080 p=0.495	r=-0.010 p=0.935	r=0.176 p=0.132	r=0.365 p=0.001	r=-0.006 p=0.957

Δ = gradient; HD = hemodialysis; HRV TAI = heart rate variability triangular index; pNN50 = percentage difference between 2 consecutive NN intervals over 50 milliseconds; r = correlation coefficient; RMSSD = root-mean square of the difference of successive R–R intervals; SDANN = standard deviation of the mean of the R–R intervals; SDNN = standard deviation of all normal R–R intervals during a 24-hour period; UF = ultrafiltration.

TABLE IV
LINEAR REGRESSION MODELS OF HRV

Dependent variables	Significant independent variables	Correlation coefficient	p Value	p Value of model
SDNN, ms	DM	-0.317	0.006	0.006
SDANN, ms	DM	-0.268	0.020	0.020
HRV TAI	DM	-0.368	0.001	0.001

DM = diabetes mellitus; HRV TAI = heart rate variability triangular index; SDANN = standard deviation of 5-minute average of normal R–R intervals; SDNN = standard deviation of all normal R–R intervals during a 24-hour period.

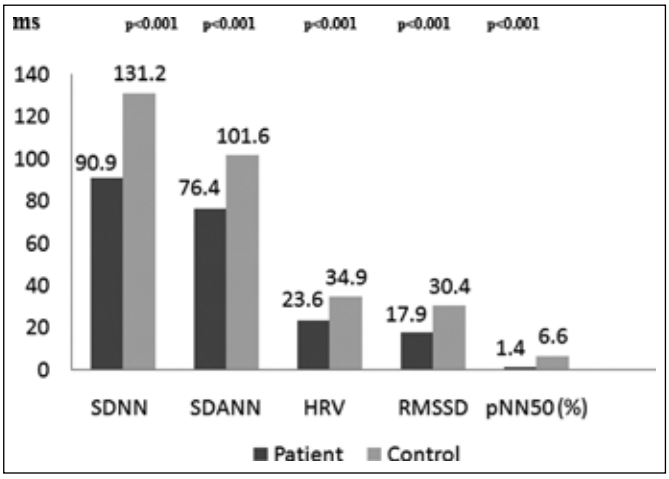

Fig. 1 - Comparison of mean heart rate variability (HRV) index data in patients and control groups. SDNN = standard deviation of all normal R–R intervals during a 24-hour period; SDANN = standard deviation of 5-minute average of normal R–R intervals; RMSSD = root-mean square of the difference of successive R–R intervals; pNN50 = number of instances per hour in which 2 consecutive R–R intervals differ by more than 50 milliseconds over 24 hours.

hypertension, diabetes and anemia, which are prevalent in CRF, can also be related to ANS dysfunction (14, 15).

In uremic cardiovascular dysautonomy, baroreceptor sensitivity and end-organ responses to vasopressor agents decrease, and changes in the sympathetic and parasympathetic tract occur. In such cases, patients tend to suffer from dialysis hypotension, chronic hypotension and arrhythmia (16, 17). In one study including 41 HD patients, the risk of atrial and ventricular arrhythmia was found to be higher in patients with autonomic dysfunction compared with those without autonomic dysfunction (18). Autonomic dysfunction is related with high mortality and sudden cardiac death in dialysis patients. Sudden cardiac death is defined as a witnessed death occurring within 1 hour of the onset of acute symptoms and without any previous condition. It would seem to be the most common cause of death in dialysis patients and is also responsible for 20%-30% of all deaths in dialysis cohort (19).

Heart rate variability is used to assess cardiac autonomic functions. HRV is a very effective and useful method for evaluating these functions because of its reproducibility and low cost. It has been demonstrated that HRV decreases in CRF patients (20-27). In our study, the time-domain parameters SDNN, SDANN, HRV, TAI, RMSSD and pNN50 (%) were found to have decreased in dialysis patients when compared with those in controls. This result was compatible with those reported in the literature, and it shows the decrease of HRV.

Age, DM, hypertension, coronary artery disease and anemia are the major parameters affecting HRV (7). In a study by Tamura et al (25), the determinants of HRV were evaluated in 187 HD patients. An ECG was recorded for 24 hours from the beginning of HD session for each patient, and SDNN was used as a marker of HRV. In multilinear regression analysis, older age, presence of diabetic nephropathy as a primary renal disease, lower hematocrit, larger body mass index, longer duration of HD and smoking were found to relate to reduced SDNN.

During the HD session, rapid electrolyte shifts and serum electrolyte level changes occur based on the electrolyte concentration gradients between the blood and dialysate. In current HD practice, dialysate is not generally individualized despite patients having a physiological dispersion of normal extracellular fluid compositions. A single dialysate prescription further aggravates serum electrolyte changes. Some studies showed that rapid electrolyte shifts may cause sudden cardiac death in HD patients (8-10).

The dialysates with low K^+ (K^+ <2 mEq/L) used for HD cause serious loss of K^+. Loss of K^+ decreases the depolarization threshold, increases QT dispersion and causes arrhythmia (27). In a multicenter study examining 502 sudden cardiac deaths, dialysate Ca lower than 2.5 mg/dL and dialysate K^+ lower than 2 mEq/L were presented as independent risk factors for sudden cardiac arrest (28). During the HD session, a positive Ca mass balance occurs (29, 30). Calcium concentration of dialysate effects intradialytic hemodynamic stability and QTc intervals (31). In a study performed in 22 HD patients, Di Iorio et al (32) reported that with a dialysate containing low K (2 mmol/L), low Ca (1.25 mmol/L) and high bicarbonate concentration (34 mmol/L), mean QTc interval was significantly prolonged compared with that recorded with dialysate containing high K (3 mmol/L), high Ca (1.75 mmol/L) and bicarbonate (30 mmol/L) (40 ± 10 milliseconds vs. 2 ± 2 milliseconds; $p<0.01$) at the end of the HD session. QT interval prolongation is associated with an increased risk of sudden death (31), thus patients who show a marked QT interval prolongation at the end of the HD session may experience a lethal arrhythmia favored by the alterations in ventricular repolarization (33).

The effects of rapid electrolyte changes during HD sessions on cardiac autonomic functions have not to date been examined in detail. Wen et al (34) evaluated the relationship between HRV parameters and electrolytes before and after HD in 23 patients. When pre- and post- HD blood samples were analyzed, a significant increase in Na and Ca concentration and a significant decrease in K and phosphorus concentration were determined. Time-domain HRV parameters (SDNN, RMSDD and NN50) and frequency domain param-

eters (low frequency, high frequency) increased significantly after HD. However, there was no correlation between electrolyte and HRV changes. The major limitation of their study is that the time for recording HRV indexes was very short. It is necessary to calculate the dates with 24-hour recordings to obtain accurate results with time-domain indexes.

In our study, there was a relationship between SDNN-pNN50 and ΔiCa^{2+} and between RMSSD and both ΔCa^{2+} and ΔiCa^{2+} in univariate analysis, but these relationships did not continue in multivariate analysis. This result supports the view that HRV is much more related to the autonomic nervous system's structural changes, especially peripheral nerves changes, than to acute electrolyte and bicarbonate changes.

Diabetic autonomic neuropathy is the most clinically important form of cardiac autonomic neuropathy and has been reported to occur in up to 70% of diabetic patients; diabetic cardiac autonomic neuropathy is associated with a high risk of cardiovascular mortality and morbidity (35, 36). HRV seems to remain the primary technique used to evaluate and quantify the cardiac risk associated with a variety of conditions in patients with DM (37). Several studies demonstrated that an increased degree of cardiac autonomic neuropathy is associated with increased prevalence of diabetic nephropathy (36). Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions (38). Several studies demonstrated that HRV is reduced in diabetic patients with silent ischemia when compared with nondiabetic individuals with cardiac events. Several studies also suggested that cardiovascular autonomic function testing provided a predictive value that could be used to identify a subgroup of patients after myocardial infarction who were at a high risk for cardiovascular death (39-43).

In our study, there was a significant relationship between DM and all of the time-domain HRV parameters. Considering these results, physicians should be alert for cases of decreased HRV, particularly in HD patients with DM.

In conclusion, CRF patients have various degrees of cardiovascular autonomic dysfunctions. These problems present themselves as decreased HRV. Uremia causes disorders which may damage ANS structures. DM, which is one of the major causes of CRF, also decreases HRV. Therefore, by maintaining optimal glycemic control and optimal dialysis conditions in patients with DM and CRF, an improvement in HRV and a decrease in the risk of sudden cardiac death may be achieved. We did not observe any significant effect of rapid electrolyte and bicarbonate changes on cardiac ANS functions.

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