Original Article

The effect of on-line hemodiafiltration on heart rate variability in end-stage renal disease

Kyung Won Park1, Sang Kyun Bae1, Buhyun Lee1, Jeong Hun Baek1, Jin Woo Park1, Sung Jin Moon2, Soo Young Yoon2,*

1 Department of Internal Medicine, Myongji Hospital, Goyang, Korea
2 Department of Internal Medicine, Kwandong University College of Medicine, Gangneung, Korea

A B S T R A C T

Background: The autonomic nervous system plays a central role in the maintenance of hemodynamic stability. Cardiac autonomic dysfunction may result in serious complications, such as sudden cardiac death. Heart rate variability (HRV) is significantly reduced in patients undergoing chronic hemodialysis (HD). The aim of this study was to evaluate the effect of on-line hemodiafiltration (OL-HDF) on the autonomic nervous system in chronic HD patients.

Methods: Forty chronic HD patients were prospectively studied. The participants were divided into conventional HD and OL-HDF groups. They received regular high-flux HD or OL-HDF for 4-hour sessions, three times a week. Time-and frequency-domain measures of the 24-hour HRV were analyzed during the interdialytic period prior to postdilution OL-HDF and every 6 months for 24 months. The 7-year survival was also evaluated.

Results: Among the 40 participants, 15 patients in the HD group and 11 patients in the OL-HDF group completed the study. There was no difference in the baseline characteristics. After 24 months of treatment, β2-microglobulin concentration decreased (from 33.4 ± 15.2 mg/dL to 28.4 ± 6.2 mg/dL, P = 0.02) in the OL-HDF group, while there was no change in the HD group. In the HRV analysis, the frequency-domain HRV parameters increased significantly compared with baseline in the OL-HDF group [natural logarithmic high frequency (lnHF), 3.15 ± 3.36 ms² vs. 4.42 ± 3.81 ms²; ln low frequency (LF), 3.56 ± 3.17 ms² vs. 4.78 ± 3.99 ms²; ln very low frequency (VLF), 4.90 ± 4.62 ms² vs. 6.38 ± 5.54 ms²; LF/HF ratio, 1.4 ± 0.4 vs. 2.5 ± 0.1]. The survival rate was similar between the groups.

Conclusion: This study shows that OL-HDF improved autonomic nervous system dysfunction in chronic HD patients.

© 2013. The Korean Society of Nephrology. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The autonomic nervous system plays a central role in the maintenance of hemodynamic stability. Cardiac autonomic dysfunction may result in serious complications, such as sudden cardiac death.
Spectral analysis of heart rate variability (HRV) has emerged in the past decade as a powerful noninvasive clinical tool for the assessment of sympathetic and parasympathetic functions of the autonomic nervous system [1]. Rubinger et al [2] reported that HRV is significantly reduced in patients undergoing chronic hemodialysis (HD), even in the absence of cardiovascular disease. Decreases in some HRV measures were suggested to be independent predictors of cardiac death during long-term follow-up in patients with end-stage renal disease receiving chronic HD [3].

On-line hemodialfiltration (OL-HDF) was introduced as a model for the effective clearance of middle-to-large molecules [4]. Compared with standard HD, OL-HDF improves hemodynamic stability and reduces mortality [5,6].

In a study with 32 dialysis patients, Laaksonen et al [7] reported that higher Kt/V ( > 1.20) was a predictor of improvement of cardiac autonomic nervous function.

The aim of this study was to evaluate the effect of OL-HDF on the autonomic nervous system in chronic HD patients. We hypothesized that OL-HDF improves the autonomic neuropathy in these patients.

Methods

Patients

Forty outpatients with end-stage renal disease were recruited who received regular chronic HD therapy for at least 3 months (4-hour sessions, three times a week, high-flux hemodialysis) at the hemodialysis room of Kwandong University Myongji Hospital between 2005 and 2006. The participants were randomized into conventional HD and OL-HDF groups. Patients with a history of any of the following medical events were excluded at baseline: myocardial infarction, stroke, a major surgical procedure within the previous 2 months, ≥NYHA 3 congestive heart failure, hemodynamically significant valvular or congenital heart disease, atrial fibillation or flutter, high grade heart block or a permanent pacemaker, chronic obstructive lung disease, severe hepatic disease, malignant neoplasms, or other physical or mental problems that limit normal daily activities. The study followed the Helsinki Declaration and Good Clinical Practices.

OL-HDF technique

OL-HDF patients received postdilution OL-HDF for 4 hours, three times weekly for 24 months with bicarbonate dialysis fluid and heparin as an anticoagulant. OL-HDF was performed using the AK200 ULTRA S (Gambro, Lund, Sweden) with nonreprocessed polyamide dialysis membranes (Polyflux 14; Gambro). Blood flow was maintained at least 250 mL/minute, the dialysate flow was 600 mL/minute, and the temperature of the dialysate was approximately 36 °C.

Laboratory methods

Blood samples were drawn every 6 months for routine laboratory assessments including hemoglobin, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, total cholesterol, triglyceride, uric acid, high sensitivity C-reactive protein, and β2-microglobulin (β2-MG). The Kt/V was calculated every 6 months for 2 years.

HRV analysis

Holter electrocardiogram (ECG) monitoring for 24 hours for power spectral analysis of the RR intervals was performed in the inter-dialytic period every 6 months for 24 months. Recorded Holter ECCs were analyzed using a Holter ECG scanner (Marquette ECG Analysis Program; GE Medical Systems, Waukesha, WI, USA), which automatically detected and labeled the QRS complexes. The results of the automatic analysis were reviewed, and errors in the R-wave detection and the QRS labeling were edited manually.

For the time-domain HRV measures, the mean normal-to-normal R-R intervals (NN) and the standard deviation of the normal-to-normal R-R intervals over the 24 hours (SDNN) measurements were calculated.

To analyze the frequency-domain HRV measures, the spectral power was quantified using fast Fourier transformation for the following frequency bands: 0.15–0.40 Hz (high frequency), 0.04–0.15 Hz (low frequency), 0.003–0.04 Hz (very-low

![Figure 1. Study population. HD, hemodialysis; OL-HDF, on-line hemodialfiltration.](image)

Table 1. Baseline characteristics of the study patients

|                   | HD (n = 15) | OL-HDF (n = 11) | P  |
|-------------------|------------|----------------|----|
| Age (y)           | 59.8 ± 6.5 | 55.7 ± 18.5    | 0.08 |
| Sex, male         | 6 (40)     | 5 (45)         | 0.57 |
| HD duration (mo)  | 38.6 ± 5.8 | 35.5 ± 9.1     | 0.34 |
| Cause of ESRD     |            |                |     |
| DM                | 10 (66.7)  | 7 (63.6)       | 0.87 |
| Hypertension      | 3 (20.0)   | 2 (18.2)       |     |
| Chronic GN        | 1 (6.7)    | 2 (18.2)       |     |
| PCKD              | 1 (6.7)    | 0              |     |
| Comorbidities     |            |                |     |
| DM                | 10 (66.7)  | 7 (63.6)       | 0.56 |
| Hypertension      | 8 (53.3)   | 6 (54.5)       | 0.75 |
| Previous ACS      | 3 (20.0)   | 2 (18.2)       | 0.16 |
| BP medications    | 8 (53.3)   | 6 (54.5)       |     |
| CCB               | 5 (62.5)   | 3 (50.0)       | 0.09 |
| Beta blocker      | 3 (37.5)   | 2 (33.3)       | 0.25 |
| ARB               | 6 (75.0)   | 4 (66.7)       | 0.10 |
| BP, mmHg          |            |                |     |
| Systolic          | 143.5 ± 21.9 | 146.3 ± 19.7 | 0.12 |
| Diastolic         | 76.7 ± 10.8 | 79.3 ± 13.2    | 0.10 |

Data are presented as n (%) or mean ± SD. ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DM, diabetes mellitus; ESRD, end-stage renal disease; GN, glomerulonephritis; HD, hemodialysis; PCKD, polycystic kidney disease.
Table 2. Changes in biochemical parameters

|                          | Hemodialysis (n = 15) | Baseline | 6 mo | 12 mo | 18 mo | 24 mo | On-line hemodiafiltration (n = 11) | Baseline | 6 mo | 12 mo | 18 mo | 24 mo    |
|--------------------------|-----------------------|----------|------|-------|-------|-------|----------------------------------|----------|------|-------|-------|----------|
| Hemoglobin (g/dL)        |                       | 10.0 ± 1.2 | 10.0 ± 1.0 | 10.1 ± 1.3 | 9.4 ± 1.1 | 9.8 ± 0.6 |                               | 9.1 ± 1.2 | 9.6 ± 1.3 | 10.3 ± 1.3 | 10.4 ± 0.6* | 10.2 ± 0.9 |
| Calcium (mg/dL)          |                       | 8.2 ± 0.6 | 8.2 ± 0.8 | 8.5 ± 0.9 | 8.4 ± 0.6 | 8.0 ± 0.7 |                               | 8.9 ± 1.4 | 8.4 ± 0.7 | 8.4 ± 0.6 | 8.2 ± 0.9 | 8.2 ± 0.8 |
| Phosphorus (mg/dL)       |                       | 4.9 ± 1.8 | 6.0 ± 1.8 | 5.1 ± 1.9 | 4.3 ± 1.3 | 5.2 ± 2.0 |                               | 4.5 ± 1.4 | 4.7 ± 1.0* | 4.2 ± 1.4 | 4.7 ± 1.2 | 5.1 ± 1.7 |
| Glucose (mg/dL)          | 190.6 ± 67.5          | 180.8 ± 65.7 | 142.9 ± 51.7 | 161.0 ± 56.0 | 159.3 ± 74.3 | | 143.0 ± 83.0          | 156.8 ± 65.3 | 139.1 ± 39.1 | 131.3 ± 39.3 | 120.3 ± 38.2 |
| BUN (mg/dL)              | 50.5 ± 17.0           | 60.1 ± 17.8 | 66.5 ± 19.1 | 61.2 ± 23.5 | 69.9 ± 18.6 | | 58.6 ± 18.1           | 48.4 ± 14.4 | 56.0 ± 11.5 | 68.3 ± 23.8 | 56.9 ± 17.9 |
| Creatinine (mg/dL)       | 8.4 ± 2.1             | 9.1 ± 2.6 | 9.6 ± 3.3 | 9.7 ± 2.0 | 10.1 ± 1.9 | | 9.2 ± 2.5             | 8.5 ± 3.0 | 8.8 ± 2.5 | 9.9 ± 3.0 | 9.9 ± 2.9 |
| Uric acid (mg/dL)        | 6.5 ± 1.0             | 6.6 ± 1.3 | 7.2 ± 1.4 | 7.2 ± 1.6 | 7.8 ± 1.5 | | 6.9 ± 1.5             | 6.6 ± 0.8 | 7.0 ± 0.8 | 7.9 ± 1.7 | 7.6 ± 1.5 |
| Total cholesterol (mg/dL)| 154.4 ± 34.7          | 149.5 ± 24.3 | 155.0 ± 58.9 | 143.6 ± 38.1 | 147.6 ± 38.9 | | 137.0 ± 26.9          | 126.1 ± 23.0 | 125.9 ± 33.0 | 130.3 ± 21.3 | 121.2 ± 24.3 |
| Albumin (g/dL)           | 3.5 ± 0.4             | 3.7 ± 0.4 | 3.7 ± 0.2 | 3.5 ± 0.5 | 3.6 ± 0.4 | | 3.3 ± 0.5             | 3.3 ± 0.5*  | 3.6 ± 0.4 | 3.5 ± 0.3 | 3.5 ± 0.5 |
| Triglyceride (mg/dL)     | 120.5 ± 50.4          | 147.3 ± 89.4 | 103.6 ± 57.9 | 72.7 ± 27.4 | 91.4 ± 4v3.4 | | 136.8 ± 92.4          | 114.1 ± 34.3 | 94.4 ± 32.4 | 114.3 ± 32.2* | 86.3 ± 22.5 |
| HDL-cholesterol (mg/dL)  | 40.4 ± 12.5           | 37.3 ± 12.0 | 37.8 ± 14.6 | 37.8 ± 13.8 | 38.4 ± 7.9 | | 32.9 ± 6.5             | 29.6 ± 4.1 | 32.7 ± 7.6 | 30.7 ± 4.3 | 30.2 ± 4.6 |
| Na (mEq/L)               | 139.3 ± 2.9           | 139.3 ± 3.2 | 140.3 ± 3.3 | 140.8 ± 3.9 | 138.5 ± 2.7 | | 141.2 ± 4.1           | 140.1 ± 2.0 | 141.3 ± 2.4 | 139.2 ± 2.6 | 141.3 ± 2.3 |
| K (mEq/L)                | 4.7 ± 1.0             | 4.9 ± 0.7 | 5.0 ± 1.7 | 5.3 ± 0.8 | 5.4 ± 0.7 | | 4.7 ± 1.3             | 4.9 ± 1.1 | 5.1 ± 0.9 | 5.2 ± 0.9 | 5.0 ± 0.8 |
| Cl (mEq/L)               | 97.5 ± 3.4            | 88.3 ± 30.5 | 101.7 ± 4.1 | 99.3 ± 2.6 | 101.4 ± 1.7 | | 99.0 ± 4.8             | 100.3 ± 13.9 | 100.0 ± 2.5 | 101.3 ± 4.3 | 99.2 ± 2.0 |
| Total CO2 (mEq/L)        | 22.9 ± 2.2            | 22.6 ± 3.6 | 21.2 ± 3.8 | 20.6 ± 3.1 | 21.8 ± 2.6 | | 23.9 ± 2.9             | 23.0 ± 1.3 | 23.4 ± 1.7 | 22.3 ± 3.3 | 23.5 ± 3.4 |
| β2-MG (mg/dL)            | 34.6 ± 16.3           | 32.3 ± 8.6 | 31.7 ± 9.9 | 33.4 ± 13.4 | 37.3 ± 9.1 | | 33.4 ± 15.2           | 25.9 ± 8.5*  | 26.3 ± 6.0*  | 26.9 ± 9.2*  | 28.4 ± 6.2*  |
| PTH (pg/mL)              | 176.3 ± 97.3          | 193.8 ± 39.1 | 188.0 ± 148.1 | 151.4 ± 134.9 | 198.4 ± 114.6 | | 190.8 ± 87.6          | 141.5 ± 53.6 | 265.0 ± 219.1 | 224.9 ± 182.1 | 220.2 ± 278.8 |
| CRP (mg/dL)              | 0.6 ± 0.9             | 0.6 ± 0.8 | 0.5 ± 0.7 | 0.8 ± 1.6 | 0.6 ± 1.1 | | 1.1 ± 1.6             | 1.7 ± 0.9 | 0.4 ± 0.4 | 0.5 ± 0.6 | 0.5 ± 0.8 |
| Kt/V                     | 1.2 ± 0.4             | 1.3 ± 0.9 | 1.3 ± 0.8 | 1.3 ± 1.4 | 1.3 ± 1.2 | | 1.2 ± 0.5             | 1.3 ± 0.8 | 1.4 ± 0.9 | 1.3 ± 0.9 | 1.3 ± 1.3 |

* P < 0.05 vs. HD.
† P < 0.05 vs. baseline.

Data are presented as mean ± SD.

β2-MG, β2-microglobulin; BUN, blood urea nitrogen; CRP, C-reactive protein; HDL, high-density lipoprotein; PTH, parathyroid hormone.
frequency), and ≤0.003 Hz (ultra-low frequency). The variances were transformed to natural logarithmic (ln) values.

**Outcome measures**

The primary outcome was improvement of autonomic neuropathy assessed with HRV, and the secondary outcome was 7-year mortality. The patients were followed for mortality analysis until December 2012 or until they received a kidney transplant. We regarded transplants as censored cases. For patients who moved to other facilities, we recruited the mortality data by telephone.

**Statistical analysis**

Continuous data are reported as the mean ± standard deviation. Categorical data are presented as absolute values and percentages. The differences between the two groups were tested using the Fisher exact or the Chi-square test for categorical variables and the Student t test or Mann–Whitney test for continuous data. The serial HRV measures were compared within and between the groups using repeated-measures analysis of variance. We performed a survival analysis using the Kaplan–Meier survival curve. All the statistical analyses were performed using SPSS software version 19.0 (IBM, Chicago, IL, USA). A 2-tailed $P < 0.05$ was considered to be statistically significant.

**Results**

Among the 40 patients, 15 patients in the HD group and 11 patients in the OL-HDF group completed the entire study (Fig. 1). Two patients died during the study period: one in the HD group from sepsis, and one in the OL-HDF group from gastric ulcer bleeding. In total, 26 patients were included in the study. The baseline characteristics are compared in Table 1. The HD and OL-HDF groups showed similar characteristics. The median age of the patients was 61 years in both groups (ranges, 49–70 years in HD group and 36–80 years in OL-HDF group). The mean dialysis vintages were 38.6 months (range, 49–125 months) and 35.3 months (range, 3–160 months) in the HD and OL-HDF groups, respectively.

The baseline laboratory findings including hemoglobin, calcium, phosphorus, blood urea nitrogen, creatinine, albumin, electrolytes, parathyroid hormone, C-reactive protein, $\beta_2$-MG, and Kt/V were not different between the HD and OL-HDF groups (Table 2).

During the 24-month follow up, $\beta_2$-MG concentration exhibited a nonsignificant increase in the HD group (34.6 ± 16.3 mg/dL to 37.3 ± 9.1 mg/dL, $P=0.060$) and a significant decrease in the OL-HDF group (33.4 ± 15.2 mg/dL to 28.4 ± 6.2 mg/dL, $P=0.013$).

**Changes of HRV parameters**

Table 3 shows the HRV parameters. The baseline HRV measures were not different between the HD and OL-HDF groups. There was no difference in the time-domain measures during the follow-up period between the HD and OL-HDF groups except for low SDNN in the HD group and high mean NN in the OL-HDF group at 24 months. The frequency-domain measures were obviously different between the two groups. The frequency-domain measures did not differ between the groups except for low SDNN in the HD group and high mean NN in the OL-HDF group. The median age of the patients was 61 years in both groups (ranges, 49–70 years in HD group and 36–80 years in OL-HDF group). The mean dialysis vintages were 38.6 months (range, 49–125 months) and 35.3 months (range, 3–160 months) in the HD and OL-HDF groups, respectively.

The baseline laboratory findings including hemoglobin, calcium, phosphorus, blood urea nitrogen, creatinine, albumin, electrolytes, parathyroid hormone, C-reactive protein, $\beta_2$-MG, and Kt/V were not different between the HD and OL-HDF groups (Table 2). During the 24-month follow up, $\beta_2$-MG concentration exhibited a nonsignificant increase in the HD group (34.6 ± 16.3 mg/dL to 37.3 ± 9.1 mg/dL, $P=0.060$) and a significant decrease in the OL-HDF group (33.4 ± 15.2 mg/dL to 28.4 ± 6.2 mg/dL, $P=0.013$).

**Table 3. Changes in heart rate variability parameters**

| Outcome measures | Time-domain measures | Frequency-domain measures | LF/HF | On-line hemodialysis (n=11) | Baseline | 6 mo | 12 mo | 18 mo | 24 mo | Baseline | 6 mo | 12 mo | 18 mo | 24 mo |
|------------------|----------------------|--------------------------|-------|---------------------------|----------|-----|-----|-----|-----|----------|-----|-----|-----|-----|
| NN (ms)          | 817.1 ± 149.2        | 804.1 ± 141.1            | 798.1 ± 134.3 | 791.3 ± 121.4 | 802.3 ± 118.3 | 12 mo | 833.3 ± 142.1 | 833.3 ± 142.1 | 822.5 ± 139.0 | 811.0 ± 131.4 | 809.1 ± 130.4 | 804.1 ± 128.4 | 802.3 ± 126.4 | 802.3 ± 124.4 | 802.3 ± 122.4 | 802.3 ± 120.4 |
| Mean NN (ms)     | 969.0 ± 274.7        | 956.0 ± 269.7            | 942.0 ± 256.7 | 941.0 ± 255.7 | 939.0 ± 254.7 | 18 mo | 981.0 ± 274.7 | 981.0 ± 274.7 | 967.0 ± 269.7 | 960.0 ± 264.7 | 956.0 ± 260.7 | 948.0 ± 255.7 | 941.0 ± 251.7 | 941.0 ± 247.7 | 939.0 ± 243.7 | 939.0 ± 239.7 |
| SDNN (ms)        | 1107 ± 30.3          | 1107 ± 30.3              | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 24 mo | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 | 1107 ± 30.3 |
| LF, ln (ms²)     | 3.24 ± 4.07          | 3.24 ± 4.07              | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 6.0 mo | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 | 3.24 ± 4.07 |
| HF, ln (ms²)     | 3.51 ± 4.07          | 3.51 ± 4.07              | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 12 mo | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 | 3.51 ± 4.07 |
| VLF, ln (ms²)    | 4.78 ± 4.07          | 4.78 ± 4.07              | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 18 mo | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 | 4.78 ± 4.07 |
| LF/HF            | 1.7 ± 0.5            | 1.7 ± 0.5                | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 24 mo | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.5 |
| Data are presented as mean ± SD. LF, low frequency; NN, normal-to-normal R-R intervals during 24 hours; HF, high frequency; VLF, very-low frequency. |
two groups at baseline but increased continuously over time in the OL-HDF group (Fig. 2).

**Survival analysis**

Five patients in the HD group and four patients in the OL-HDF group transferred to other facilities after the study completion. Among patients who stayed at our hospital, seven in the HD group and four in the OL-HDF group maintained their HD modality without change.

Five patients in the HD group (45.5%) and seven patients in the OL-HDF group (46.7%) died during the follow-up period. The Kaplan–Meier survival curve showed that the cumulative survival was not different between the groups (Fig. 3).

**Discussion**

The major finding of our study was that OL-HDF improved autonomic nervous system dysfunction measured by HRV in chronic HD patients.

Many HD patients have autonomic neuropathy. Ewing DJ and Winney R [8] found that half of the HD patients exhibited autonomic neuropathy using three simple methods including responses to the Valsalva maneuver, handgrip response, and beat-to-beat variation of the heart beat at rest. Several studies have reported that hypotension during HD may be caused by autonomic neuropathy [9–11]. Many of HD patients without intradialytic hypotension also experience autonomic neuropathy symptoms including impotence, postural dizziness, and uremic pruritus [12–14].

Analysis of HRV has been used as a noninvasive tool to assess the autonomic nervous system. Although there are various ways of quantifying HRV, including time domain, frequency domain, and nonlinear analysis, one method has not been established as superior to another [15–17]. Recently, Suzuki et al [18] reported that nonlinear measures of HRV had predictive value for mortality in HD patients. We analyzed HRV conventionally using 24-hour Holter ECGs for time and frequency domain analyses according to the guidelines [19].

Uremic cardiac autonomic neuropathy may be characterized by reduced HRV indicating cardiac sympathetic overactivity and parasympathetic deterioration [20]. Several studies have reported reduced HRV [21] and its association with left ventricular hypertrophy [22] and increased CKD-related hospitalization [23].

The role of dialysis in autonomic neuropathy has been reported by several investigators. Leem et al [24] reported that dialysis did not alter autonomic nerve function during the first 12 months of HD. However, Laaksonen et al [7] found that the improvement in HRV occurred only in patients who had a Kt/V > 1.2. Progressive deterioration of autonomic neuropathy was associated with a Kt/V < 0.87. In addition, Dursun et al [25] suggested that dialysis for 12 months improved autonomic dysfunction, especially in continuous ambulatory peritoneal dialysis (CAPD).

Genovesi et al [26] suggested a potential autonomic advantage with convective treatment (hemofiltration) compared with diffusive treatment (hemodialysis) during both interdialytic and intradialytic periods using spectral analysis of HRV. The role of convection in treatment of autonomic neuropathy is not fully understood. Santoro et al [27] suggested that hemofiltration acts through less negative sodium balance and effective removal of vasodilating or autonomic nervous inhibitory substances. In the present study, OL-HDF for 24 months improved autonomic neuropathy measured by HRV analysis. It is well known that many patients with systemic amyloidosis have autonomic neuropathy and they show abnormal HRV [28,29]. Most uremic patients have high β2-MG concentration and this causes uremic amyloidosis. In our study,
OL-HDF effectively removed β2-MG with the convective method; however, we cannot find any causal relationship between β2-MG and autonomic neuropathy. Rubinger et al. [2] reported that renal transplantation normalized HRV in most uremic patients except the amyloidosis patients with cardiac or adrenal involvement. However, they did not reveal the relationship between β2-MG and HRV.

In contrast to previous studies, we failed to show improved survival in the patients treated with OL-HDF [6,30]. The small study population and the inability of some patients to maintain their HD modality after moving to other hospitals might be barriers to confirming improved survival.

Our study has several limitations. First, the sample size was small and the study was performed at a single center. It is well known that the majority of HD patients are diabetics and abnormal HD is very common in patients with diabetes regardless of renal function [31,32]. Unfortunately, because of the small sample size, we could not compare the effect of OL-HDF on HRV in diabetics with nondiabetics. Second, we recorded Holter electrocardiography during the interdialytic period, which may not incorporate intradialytic arrhythmia. Third, we were unable to obtain information concerning the HD modality, (i.e., HD vs. OL-HDF) in the patients who were transferred to other facilities.

To our knowledge, this is the first prospective study to examine the effect of OL-HDF on autonomic neuropathy in chronic HD patients. Large-scale studies are required to confirm the role of OL-HDF in the improvement of autonomic neuropathy in HD patients.

**Conflicts of interest**

The authors have no conflicts of interest to declare.

**Acknowledgments**

We thank Ms. Mira Yoon for her technical assistance in the HRV analysis.

**References**

[1] Ranpuria R, Hall M, Chan CT, Unruh M: Heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV. *Nephrol Dial Transplant* 23:444–449, 2008

[2] Rubinger D, Sapoznikov D, Pollak A, Popovtzer MM, Luria MH: Heart rate variability during chronic hemodialysis and after renal transplantation: studies in patients without and with systemic amyloidosis. *J Am Soc Nephrol* 10:1972–1981, 1999

[3] Fukuta H, Hayano J, Ishihara S, Sakata S, Mukai S, Ohte N, Ojika K, Yagi K, Matsumoto H, Suhimya S, Kimura G: Prognostic value of heart rate variability in patients with end-stage renal disease on chronic haemodialysis. *Nephrol Dial Transplant* 18:318–325, 2003

[4] Canaud B, Flavier JL, Argillés A, Stec F, Bouloux QV NG, Garred C, Mion LJ: C: Hemodialfiltration with on-line production of substitution fluid: long-term safety and quantitative assessment of efficacy. *Contrib Nephrol* 108:12–22, 1994

[5] Maduell F, del Pozo C, Garcia H, Sanchez L, Hdez-Jaras J, Albero MD, Calvo C, Torregrosa I, Navarro V: Change from conventional haemodiafiltration to on-line haemodiafiltration. *Nephrol Dial Transplant* 14:1202–1207, 1999

[6] Maduell F, Moreo F, Pons M, Ramos R, Mora-Macia J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A: ESHOL Study Group: High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol* 24:487–497, 2013

[7] Laaksonen S, Voipio-Pulkki L, Erkinjuntti M, Asola M, Fälck E: Does dialysis therapy improve autonomic and peripheral nervous system abnormalities in chronic uremia? *J Intern Med* 248:21–26, 2000

[8] Ewings D, Winney R: Autonomic function in patients with chronic renal failure on intermittent haemodialysis. *Nephron* 15:424–429, 1975

[9] Kersh ES, Kronfeld SJ, Unger A, Popper RW, Cantor S, Cohn K: Autonomic insufficiency in uremia as a cause of hemodialysis-induced hypotension. *N Engl J Med* 290:650–653, 1974

[10] Lilley JJ, Golden J, Stone RA: Adrenergic regulation of blood pressure in chronic renal failure. *J Clin Invest* 57:1190–1200, 1976

[11] Yang NL, Wang CH, Hung MJ, Chen YC, Wu IW, Lee CC, Wu MS, Kuo JT, Cheng CW, Cheng WJ: Real-time three-dimensional echocardiography provides advanced haemodynamic information associated with intra-dialytic hypotension in patients with autonomic dysfunction. *Nephrol Dial Transplant* 25:249–254, 2010

[12] Vita G, Bellingeri G, Truso A, Costantino G, Santoro D, Monteleone F, Messina C, Savica V: Uremic autonomic neuropathy studied by spectral analysis of heart rate. *Kidney Int* 56:232–237, 1999

[13] Wang SJ, Liao KK, Liou HH, Lee SS, Tsai CP, Lin KP, Kao KP, Wu ZA: Sympathetic skin response and R-R interval variation in chronic uremic patients. *Muscle Nerve* 17:411–418, 1994

[14] Zakrzewska-Pniewska B, Jedras M: Is pruritus in chronic uremic patients related to peripheral somatic and autonomic neuropathy? Study by R-R interval variation test (RRIV) and by sympathetic skin response (SSR) *Neurophysiol Clin* 31:181–193, 2001

[15] ROUTLEDGE HC, CHOWDHARY S, TOWNEND JN: Heart rate variability—a therapeutic target? *J Clin Pharm Ther* 27:85–92, 2002

[16] Reed MJ, Robertson CE, Addison PS: Heart rate variability measurements and the prediction of ventricular arrhythmias. *QJM* 98:87–95, 2005

[17] Kleger RE, Stein PK, Bigger JT: Jr: Heart rate variability: measurement and clinical utility. *Ann Noninvasive Electrocardiol* 10:88–101, 2005

[18] Suzuki M, Hiroshi T, Aoyama T, Tanaka M, Ishii H, Kishohara M, Iizuka N, Murohara T, Hayano J: Nonlinear measures of heart rate variability and mortality risk in hemodialysis patients. *Clin J Am Soc Nephrol* 7:1454–1460, 2012

[19] Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 93:1043–1065, 1996.

[20] Kurata C, Uehara A, Sugiy T, Ishikawa A, Fujita K, Yonemura K, Hishida A, Ishikawa K, Tawarara H, Shouda S, Mikami T: Cardiac autonomic neuropathy in patients with chronic renal failure on hemodialysis. *Nephron* 84:312–319, 2000

[21] Di Leo R, Vita G, Messina C, Savica V: Autonomic function in elderly uremics studied by spectral analysis of heart rate. *Kidney Int* 67:1521–1525, 2005

[22] Nishimura M, Hashimoto T, Kobayashi H, Fukuda T, Okino K, Yamamoto N, Nakamura N, Yoshikawa T, Takahashi H, Ono T: Association between cardiovascular autonomic neuropathy and left ventricular hypertrophy in diabetic haemodialysis patients. *Nephrol Dial Transplant* 19:2532–2538, 2004

[23] Brotman DJ, Bash LD, Qayyum R, Crews D, Whitsel EA, Astor BC, Coresh J: Heart rate variability predicts ESRD and CKD-related hospitalization. *J Am Soc Nephrol* 21:1560–1570, 2010

[24] Leem J, Kim H, Kwon SG, Park YS, You IY, Hong ES, Earm J, Lee H, Lee KM: Change of autonomic and peripheral nerve function after the first twelve months of dialysis in end-stage renal disease. *Korean J Nephrol* 21:807–814, 2002

[25] Dursun B, Demircioglu F, Varan HI, Kabukcu M, Ersoy F, Ersel F, Suleymanlar G: Effects of different dialysis modalities on cardiac autonomic dysfunctions in end-stage renal disease patients: one year prospective study. *Ren Fail* 26:35–38, 2004

[26] Genovesi S, Bracci O, Fabbrini P, Lussetto E, Viganò MR, Lucini D, Malacarne M, Stella A, Pagani M: Differences in heart rate
variability during haemodialysis and haemofiltration. Nephrol Dial Transplant 22:2256–2262, 2007

[27] Santoro A, Mancini E, Zucchelli P: The impact of haemofiltration on the systemic cardiovascular response. Nephrol Dial Transplant;15(Suppl 2):49–54, 2000

[28] Zhao Y, Hörnsten R, Lindqvist P, Wiklund U, Suhr OB, Henein MY: Left ventricular dyssynchrony is associated with reduced heart rate variability in familial amyloidotic polyneuropathy. Int J Cardiol 155:273–278, 2012

[29] Nussinovitch U, Volovitz B, Nussinovitch M, Lidar M, Feld O, Nussinovitch N, Livneh A: Abnormal heart rate variability in AA amyloidosis of familial Mediterranean fever. Amyloid 18:206–210, 2011

[30] Ok E, Asci G, Toz H, Ok ES, Kirceli F, Yilmaz M, Hur E, Demirci MS, Demirci C, Duman S, Basci A, Adam SM, Isik IO, Zengin M, Suleymanlar G, Yilmaz ME, Ozkahya M: Turkish Online Haemofiltration Study: Mortality and cardiovascular events in online haemofiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant 28:192–202, 2013

[31] Khoharo HK, Halepoto AW: QTc-interval, heart rate variability and postural hypotension as an indicator of cardiac autonomic neuropathy in type 2 diabetic patients. J Pak Med Assoc 62:328–331, 2012

[32] Mylonopoulou M, Tentolouris N, Antonopoulos S, Mikros S, Katsaros K, Melidonis A, Sevastos N, Katsilambros N: Heart rate variability in advanced chronic kidney disease with or without diabetes: midterm effects of the initiation of chronic haemodialysis therapy. Nephrol Dial Transplant 25:3749–3754, 2010