Original Paper

Heart Rate Variability Predicts Major Adverse Cardiovascular Events and Hospitalization in Maintenance Hemodialysis Patients

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Key Words

Heart rate variability • Very low frequency • Hemodialysis • Major adverse cardiovascular events • Hospitalization

Abstract

Background/Aims: Heart rate variability (HRV) has been linked to mortality in maintenance hemodialysis (HD) patients, but it is less clear whether HRV is associated with major adverse cardiovascular events (MACEs) and hospitalization. **Methods:** This study enrolled 179 maintenance HD patients. HRV was measured to assess its prognostic significance in relation to MACEs and hospitalization. **Results:** During the follow-up period of 33.3 ± 6.7 months, 36 (20.1%) patients had a MACE, and 98 (54.7%) experienced hospitalization. In multivariate adjusted Cox regression analysis, low very low frequency (VLF) power (hazard ratio [HR], 0.727; 95% confidence interval [CI], 0.624–0.848; $p < 0.001$), a history of coronary artery disease, high ultrafiltration rate, the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and the use of beta-blockers were all significantly associated with MACEs. Low VLF power (HR, 0.873; 95% CI, 0.785–0.971; $p = 0.012$), low serum albumin, low serum creatinine, low Kt/V levels, and high serum calcium-phosphorus product levels significantly predicted hospitalization in maintenance HD patients. **Conclusions:** Reduced VLF power is linked to an increased risk of MACEs and hospitalization in maintenance HD patients. Assessing cardiac autonomic function through HRV is of pivotal prognostic significance for this patient population.

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Introduction

End-stage renal disease (ESRD) has emerged as a major healthcare problem worldwide, with the number of sufferers growing rapidly. Not only does ESRD carry a high risk of both morbidity and mortality, but also poses a significant economic burden [1]. In particular, major adverse cardiovascular events (MACEs) are the leading cause of mortality and disability among patients with ESRD [1, 2]. The factors contributing to the increase in ESRD-related MACEs and mortality are complex and remain unclear. Traditional risk factors, such as aging, diabetes, hypertension, and dyslipidemia, contribute to a certain proportion of the pathophysiology of adverse cardiovascular (CV) outcomes. However, uremia-related disorders, including inflammation, oxidative stress, accelerated arterial stiffness, and autonomic dysfunction, appear to play an essential role in the development of MACEs [3].

Sympathetic overactivity and depressed vagal modulation have been reported in patients with chronic kidney disease (CKD) and those require maintenance dialysis [4]. As one plausible risk factor, cardiac autonomic function can be measured noninvasively using heart rate variability (HRV). Although HRV is conventionally assessed by 24-hour ambulatory electrocardiography (ECG), shorter ECG recordings have also been conveniently used in clinical practice [5-7]. The association between HRV and mortality has been established in various populations [8, 9]. Furthermore, decreased HRV has been demonstrated to be an independent predictor of mortality and sudden death in maintenance hemodialysis (HD) patients [10-12]. Hence, HRV measurements may provide risk-stratification values for identifying high-risk patients early.

Patients who experienced a MACE or hospitalization tend to be disabled and succumb, and this has both clinical and economic implications. Although HRV has predictive significance for death in chronic HD patients, it remains unclear whether reduced HRV is linked to an increased risk of MACEs or hospitalization. Therefore, we investigated the associations of HRV with MACEs and hospitalization based on 5-minute ECG recordings of maintenance HD patients.

Materials and Methods

Ethics statement

The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital. Informed consent was obtained from all patients who participated. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

Study patients and design

This prospective cohort study was conducted in the dialysis unit of a regional hospital in Taiwan. All 220 patients receiving HD treatment three times a week in this hospital were included, except for 6 patients with refusal of study, 27 patients receiving nighttime HD treatment, one patient with an implanted cardiac pacemaker, and 4 patients with a history of atrial fibrillation or presence of atrial fibrillation in ECG. Each HD session was performed for 3.5 to 4 hours using a dialyzer with blood flow rates ranging from 250 to 300 mL/min and a dialysate flow rate of 500 mL/min. Between May 2012 and July 2012, 182 maintenance HD patients were enrolled in the study, with follow-up continuing until June 30, 2015. Three patients with missing data were excluded. Ultimately, a total of 179 patients were included and analyzed (Fig. 1).

Electrocardiogram signal processing

Before receiving HD treatment, study patients were instructed to lie quietly and breathe normally in the supine position for at least 10 minutes. Subsequently, 5 minutes of supine resting ECG recordings were collected for HRV analysis before the mid-week HD treatment. ECG signals were recorded using an HRV analyzer (SS1C, Enjoy Research Inc., Taipei, Taiwan) with an analog-to-digital converter at a sampling rate of 256 Hz. Digitized ECG signals were analyzed online and simultaneously stored on a hard disk for offline verification. Signal acquisition, storage, and processing were all performed on an IBM-compatible portable

personal computer. The computer algorithm then identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood in a standard QRS template. Stationary R-R values were resampled and interpolated at a rate of 7.11 Hz to produce continuity in the time domain [13].

HRV frequency domain analysis

Detailed measurements for HRV analysis have been reported previously [5]. Frequency domain analysis was performed using a nonparametric method of fast Fourier transformation (FFT). The direct current component was deleted, and a Hamming window was used to attenuate the leakage effect [14]. For each time segment (288 s; 2048 data points), our algorithm estimated the power spectrum density based on FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window. The power spectrum was subsequently quantified into standard frequency domain measurements, including very low frequency (VLF) (0.003–0.04 Hz), low frequency (LF) (0.04–0.15 Hz), high frequency (HF) (0.15–0.40 Hz), and LF/HF ratio HRV [5].

The values of each power spectrum were expressed in natural logarithmic form to obtain a normal distribution.

Collection of demographic, medical, and laboratory data

Demographic and medical data, including age, gender, current smoking habits, and comorbid conditions, were obtained from medical records and interviews with patients. Major nephrological diagnoses, including diabetic kidney disease, non-diabetic glomerular disease, and others were obtained from medical records and chart reviews. Venous blood was collected following overnight fasting by using an autoanalyzer (Roche Diagnostics GmbH, D-68298 Mannheim COBAS Integra 400) for measuring various biomarkers: albumin, fasting blood glucose, serum triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin, high-sensitivity C-reactive protein (hs-CRP), creatinine, potassium, total calcium, and phosphorus. Serum intact PTH (iPTH) concentrations were evaluated using a commercially available two-sided immunoradiometric assay (CIS Bio International, France). Blood samples were obtained within one month of study enrollment. The time of reading laboratory biomarkers was along with study patients' ECG recordings, and these data were analyzed cross-sectionally at baseline. Ultrafiltration rate was defined as ultrafiltration divided by body weight. Single-pool Kt/V was evaluated as a marker of dialysis efficiency and determined according to the Daugirdas procedure [15].

Outcomes

Two clinical outcomes, MACEs and hospitalization, were assessed. MACEs were ascertained by reviewing charts and defined as follows: hospitalization for unstable angina, nonfatal myocardial infarction, sustained ventricular arrhythmia, hospitalization for congestive heart failure, transient ischemia attack or stroke, and hospitalization for peripheral artery occlusive disease, and death by aforementioned causes. Model

Fig. 1. Flowchart of participants analyzed in this study.

for MACEs was censored at the development of MACEs or the end of the follow-up. Model for hospitalization was censored when patients had hospitalization from any cause or at the end of the follow-up.

Statistical analysis

Statistical analysis was performed using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows. Data are expressed as percentages, mean $\pm$ standard deviation, or mean $\pm$ standard error of the mean for HRV parameters, or median (25th–75th percentile) for dialysis vintage, serum triglycerides, hs-CRP, and iPTH levels. The differences in HRV between groups were analyzed using independent *t*-test. Time to clinical outcomes, including MACEs and hospitalization, and covariates of risk factors were modeled using the Cox proportional hazards model. Covariates were

Table 1. Baseline characteristics of patients with and without MACEs

Characteristics	All patients (n = 179)	Without MACEs (n = 143)	With MACEs (n = 36)
Age (year)	61.2 $\pm$ 11.4	60.6 $\pm$ 11.6	63.3 $\pm$ 10.4
Male gender (%)	44.7	43.4	50.0
Current smoker (%)	4.5	2.8	11.1
Dialysis vintage (years)	6.0 (2.4–10.3)	6.3 (2.4–10.8)	5.3 (3.3–9.3)
Diabetes mellitus (%)	45.8	42.0	61.1*
Hypertension (%)	62.6	58.7	77.8*
Congestive heart failure (%)	24.6	23.1	30.6
Coronary artery disease (%)	26.8	22.4	44.4*
Cerebrovascular disease (%)	16.2	13.3	27.8*
Underlying kidney disease			
Diabetic kidney disease (%)	44.1	41.2	55.6
Non-diabetic glomerular disease (%)	45.3	49.0	30.6*
Others (%)	10.6	9.8	14.8
Systolic BP before dialysis (mmHg)	152.7 $\pm$ 26.5	150.5 $\pm$ 26.0	161.1 $\pm$ 27.0*
Diastolic BP before dialysis (mmHg)	81.6 $\pm$ 14.3	81.1 $\pm$ 14.6	83.6 $\pm$ 13.1
Ultrafiltration rate (%)	4.2 $\pm$ 1.4	4.1 $\pm$ 1.4	4.9 $\pm$ 1.3*
Duration of HD treatment (minutes)	237.8 $\pm$ 9.2	237.4 $\pm$ 10.2	239.2 $\pm$ 3.5
Laboratory parameters			
Albumin (g/dL)	3.8 $\pm$ 0.3	3.9 $\pm$ 0.3	3.8 $\pm$ 0.2
Fasting glucose (mg/dL)	117.9 $\pm$ 42.0	111.1 $\pm$ 39.6	144.1 $\pm$ 69.8*
Triglycerides (mg/dL)	131 (92–210)	126 (90–203)	143 (102–224)
Total cholesterol (mg/dL)	182.5 $\pm$ 42.0	182.1 $\pm$ 42.1	184.0 $\pm$ 42.3
HDL-C (mg/dL)	41.1 $\pm$ 11.0	41.6 $\pm$ 11.0	39.1 $\pm$ 10.8
LDL-C (mg/dL)	97.1 $\pm$ 33.3	98.2 $\pm$ 33.9	92.9 $\pm$ 30.8
Hemoglobin (g/dL)	10.2 $\pm$ 1.1	10.2 $\pm$ 1.1	10.3 $\pm$ 1.2
hs-CRP (mg/L)	2.7 (1.0–6.5)	2.4 (0.9–6.5)	3.3 (1.7–6.8)
Creatinine (mg/dL)	9.7 $\pm$ 2.1	9.7 $\pm$ 2.2	9.7 $\pm$ 1.9
Potassium (mmol/L)	4.5 $\pm$ 0.7	4.5 $\pm$ 0.8	4.5 $\pm$ 0.6
Total calcium (mg/dL)	9.4 $\pm$ 1.0	9.3 $\pm$ 1.0	9.6 $\pm$ 1.1
Phosphorus (mg/dL)	4.5 $\pm$ 1.0	4.4 $\pm$ 1.0	4.7 $\pm$ 1.1
Calcium-phosphorus product (mg ² /dL ²)	41.8 $\pm$ 10.9	40.8 $\pm$ 10.1	45.8 $\pm$ 12.9*
iPTH (pg/mL)	357 (188–487)	340 (184–462)	450 (227–650)
Kt/V (Daugirdas)	1.6 $\pm$ 0.2	1.6 $\pm$ 0.2	1.6 $\pm$ 0.2
Medications			
ACE inhibitors or ARBs (%)	16.8	12.6	33.3*
Beta-blockers (%)	17.3	12.6	36.1*
Calcium channel blockers (%)	19.6	16.8	30.6
Statins (%)	17.3	15.4	25.0
HRV parameters (frequency domain)			
VLF (ln ms ²)	4.07 $\pm$ 0.12	4.25 $\pm$ 0.11	3.35 $\pm$ 0.37*
LF (ln ms ²)	2.29 $\pm$ 0.29	2.46 $\pm$ 0.29	1.64 $\pm$ 0.83
HF (ln ms ²)	2.20 $\pm$ 0.32	2.32 $\pm$ 0.33	1.71 $\pm$ 0.92
LF/HF ratio	0.09 $\pm$ 0.09	0.14 $\pm$ 0.10	-0.07 $\pm$ 0.25

* *p* value < 0.05 compared to patients without MACEs. Abbreviations: MACE, major adverse cardiovascular event; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; HRV, heart rate variability; VLF, very low frequency; LF, low frequency; HF, high frequency

selected into multivariate Cox models if their *P* value was < 0.05 in univariate analysis. The survival curves for the clinical outcomes were derived using Kaplan–Meier analysis. *P* value < 0.05 was considered statistically significant.

Results

A total of 179 HD patients were included and analyzed in the present study. Table 1 presents the baseline characteristics of study patients with and without MACEs. The mean age was 61.2 $\pm$ 11.4 years, and 80 (44.7%) patients were men. The dialysis vintage was 6.0 (25th–75th percentile range, 2.4–10.3) years. The HRV parameters for the patients were VLF of 4.07 $\pm$ 0.12 ln ms², LF of 2.29 $\pm$ 0.29 ln ms², HF of 2.20 $\pm$ 0.32 ln ms², and LF/HF ratio

of 0.09 ± 0.09 . Compared with patients without MACEs, those with MACEs tended to have a higher prevalence of diabetes, hypertension, coronary artery disease, and cerebrovascular disease, a lower prevalence of non-diabetic glomerular disease, a higher systolic blood pressure (BP), higher ultrafiltration rate, higher fasting glucose and serum calcium-phosphorus product levels, a higher proportion of receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and beta-blockers, and a lower level of VLF power.

Table 2 displays the baseline characteristics of study patients with and without hospitalization. Compared with patients without hospitalization, those with hospitalization tended to have higher fasting glucose and triglycerides, lower serum albumin and creatinine levels, and a lower level of VLF power.

Table 3 shows the baseline characteristics of study patients stratified according to tertiles of VLF power. Compared with patients in the lowest tertile of VLF, those in the highest tertile of VLF were more likely to have a longer dialysis vintage, lower prevalence of diabetes and diabetic kidney disease, lower systolic and diastolic BP, and lower rate of hospitalization.

Table 2. Baseline characteristics of patients with and without hospitalization

Characteristics	Without hospitalization (n = 81)	With hospitalization (n = 98)
Age (year)	60.8 ± 10.5	61.4 ± 12.2
Male gender (%)	42.0	46.9
Current smoker (%)	3.7	5.1
Dialysis vintage (years)	6.0 (2.5–10.4)	6.0 (2.1–10.2)
Diabetes mellitus (%)	40.7	50.0
Hypertension (%)	64.2	61.2
Congestive heart failure (%)	21.0	27.6
Coronary artery disease (%)	22.2	30.6
Cerebrovascular disease (%)	14.8	17.3
Underlying kidney disease		
Diabetic kidney disease (%)	40.7	46.9
Non-diabetic glomerular disease (%)	50.6	40.8
Others (%)	8.6	12.2
Systolic BP before dialysis (mmHg)	149.9 ± 28.0	155.0 ± 25.1
Diastolic BP before dialysis (mmHg)	79.8 ± 14.1	83.1 ± 14.4
Ultrafiltration rate (%)	4.1 ± 1.4	4.4 ± 1.5
Duration of HD treatment (minutes)	238.8 ± 6.3	236.9 ± 11.0
Laboratory parameters		
Albumin (g/dL)	3.9 ± 0.3	3.8 ± 0.3*
Fasting glucose (mg/dL)	106.4 ± 39.3	127.1 ± 54.1*
Triglycerides (mg/dL)	124 (93–178)	141 (92–240)*
Total cholesterol (mg/dL)	182.7 ± 38.1	182.3 ± 45.1
HDL-C (mg/dL)	42.2 ± 10.9	40.1 ± 10.9
LDL-C (mg/dL)	99.5 ± 29.7	95.1 ± 36.0
Hemoglobin (g/dL)	10.2 ± 0.9	10.3 ± 1.3
hs-CRP (mg/L)	1.7 (0.8–5.1)	3.4 (1.4–8.1)
Creatinine (mg/dL)	10.0 ± 1.9	9.4 ± 2.3*
Potassium (mmol/L)	4.6 ± 0.7	4.4 ± 0.7
Total calcium (mg/dL)	9.3 ± 1.0	9.4 ± 1.0
Phosphorus (mg/dL)	4.3 ± 1.0	4.6 ± 1.1
Calcium-phosphorus product (mg ² /dL ²)	40.3 ± 9.9	43.1 ± 11.5
iPTH (pg/mL)	365 (186–471)	344 (188–555)
Kt/V (Daugirdas)	1.7 ± 0.3	1.6 ± 0.2
Medications		
ACE inhibitors or ARBs (%)	19.8	14.3
Beta-blockers (%)	14.8	19.4
Calcium channel blockers (%)	21.0	18.4
Statins (%)	18.5	16.3
HRV parameters (frequency domain)		
VLF (ln ms ²)	4.38 ± 0.15	3.81 ± 0.17*
LF (ln ms ²)	2.31 ± 0.49	2.28 ± 0.34
HF (ln ms ²)	2.08 ± 0.56	2.30 ± 0.37
LF/HF ratio	0.23 ± 0.14	-0.02 ± 0.12

* p value < 0.05 compared to patients without hospitalization. Abbreviations are the same as in Table 1

Predictors of MACEs

During the mean follow-up period of 33.3 ± 6.7 months, 36 MACEs were documented in our patients. These included fatal CV deaths (n = 11), hospitalization for unstable angina or nonfatal myocardial infarction (n = 10), hospitalization for congestive heart failure (n = 5), transient ischemic attack or stroke (n = 9), and peripheral arterial occlusive disease (n = 1). In multivariate forward Cox proportional hazards model, coronary artery disease (hazard ratio [HR], 2.047; 95% confidence interval [CI], 1.034–4.052; $p = 0.040$), high ultrafiltration rate (HR, 1.543; 95% CI, 1.204–1.978; $p = 0.001$), use of ACE inhibitors or ARBs (HR, 2.960; 95% CI, 1.291–6.786; $p = 0.010$), and use of beta-blockers (HR, 2.215; 95% CI, 1.021–4.808; $p = 0.044$) were all associated with an increase in MACEs. In addition, low VLF power (HR,

Table 3. Baseline characteristics stratified according to tertiles of VLF power

Characteristics	Tertile 1 ($< 3.75 \ln \text{ms}^2$) n = 58	Tertile 2 ($3.75\text{--}4.61 \ln \text{ms}^2$) n = 61	Tertile 3 ($> 4.61 \ln \text{ms}^2$) n = 60	p value
Age (year)	62.1 $\pm$ 10.9	62.4 $\pm$ 10.0	58.9 $\pm$ 13.0	0.181
Male gender (%)	51.7	44.3	38.3	0.342
Current smoker (%)	3.4	4.9	5.0	0.900
Dialysis vintage (years)	4.3 (2.1–6.8)	5.8 (2.6–9.7)	9.3 (2.4–12.8)*	0.001
Diabetes mellitus (%)	62.1	44.3	31.6*	0.004
Hypertension (%)	67.2	50.8	70.0	0.062
Congestive heart failure (%)	27.6	23.0	23.3	0.810
Coronary artery disease (%)	31.0	21.3	39.5	0.463
Cerebrovascular disease (%)	24.1	13.1	11.7	0.133
Underlying kidney disease				
Diabetic kidney disease (%)	60.3	42.6	30.0*	0.004
Non-diabetic glomerular disease (%)	37.9	45.9	51.6	0.323
Others (%)	1.7	11.5	18.3*	0.013
Systolic BP before dialysis (mmHg)	161.5 $\pm$ 26.5	151.2 $\pm$ 26.0	145.7 $\pm$ 24.9*	0.005
Diastolic BP before dialysis (mmHg)	86.0 $\pm$ 14.0	81.7 $\pm$ 14.7	77.2 $\pm$ 13.0*	0.004
Ultrafiltration rate (%)	4.1 $\pm$ 1.6	4.4 $\pm$ 1.3	4.2 $\pm$ 1.5	0.612
Duration of HD treatment (minutes)	238.9 $\pm$ 8.5	237.3 $\pm$ 8.9	237.2 $\pm$ 10.3	0.376
Laboratory parameters				
Albumin (g/dL)	3.8 $\pm$ 0.3	3.9 $\pm$ 0.3	3.9 $\pm$ 0.3	0.355
Fasting glucose (mg/dL)	131.6 $\pm$ 60.1	113.2 $\pm$ 41.2	110.0 $\pm$ 42.8	0.041
Triglycerides (mg/dL)	151 (94–232)	119 (87–219)	121 (99–175)	0.189
Total cholesterol (mg/dL)	186.9 $\pm$ 44.5	176.4 $\pm$ 44.3	184.4 $\pm$ 36.7	0.362
HDL-C (mg/dL)	39.9 $\pm$ 10.3	42.2 $\pm$ 12.0	41.1 $\pm$ 10.6	0.506
LDL-C (mg/dL)	98.7 $\pm$ 35.0	91.6 $\pm$ 33.9	101.1 $\pm$ 30.5	0.267
Hemoglobin (g/dL)	10.5 $\pm$ 1.1	10.1 $\pm$ 1.1	10.1 $\pm$ 1.1	0.172
hs-CRP (mg/L)	3.2 (1.4–7.9)	2.6 (1.4–6.1)	1.9 (0.8–5.6)	0.887
Creatinine (mg/dL)	9.3 $\pm$ 2.2	9.8 $\pm$ 2.0	10.0 $\pm$ 2.1	0.199
Potassium (mmol/L)	4.4 $\pm$ 0.7	4.5 $\pm$ 0.6	4.6 $\pm$ 0.9	0.176
Total calcium (mg/dL)	9.4 $\pm$ 0.9	9.3 $\pm$ 0.9	9.4 $\pm$ 1.3	0.807
Phosphorus (mg/dL)	4.5 $\pm$ 1.1	4.4 $\pm$ 1.0	4.6 $\pm$ 1.0	0.404
Calcium-phosphorus product (mg^2/dL^2)	41.9 $\pm$ 11.7	40.3 $\pm$ 10.7	43.4 $\pm$ 10.1	0.310
iPTH (pg/mL)	349 (210–476)	343 (171–469)	368 (186–644)	0.121
Kt/V (Daugirdas)	1.6 $\pm$ 0.3	1.6 $\pm$ 0.2	1.7 $\pm$ 0.2	0.216
Medications				
ACE inhibitors or ARBs (%)	19.0	11.5	20.0	0.392
Beta-blockers (%)	22.4	13.1	16.7	0.402
Calcium channel blockers (%)	20.7	14.8	23.3	0.476
Statins (%)	15.5	19.7	16.7	0.825
Outcomes				
MACEs (%)	31.0	13.1*	16.6	0.037
Hospitalization (%)	69.0	54.0	41.7*	0.012
CV events (%)	35.0	12.1	28.0	0.078
GI disorders or bleeding (%)	2.5	21.2	12.0	0.041
Infectious diseases or sepsis (%)	40.0	30.3	28.0	0.537
Malignancy (%)	10.0	15.2	24.0	0.312
Musculoskeletal disorders or fractures (%)	7.5	9.1	0	0.322
AV access complications (%)	0	6.1	4.0	0.311
Others (%)	5.0	6.1	4.0	0.939

* $p < 0.05$ in comparison with tertile 1 of VLF. Abbreviations: CV, cardiovascular; GI, gastrointestinal; AV, arteriovenous. Other abbreviations are the same as in Table 1

0.727; 95% CI, 0.624–0.848; $p < 0.001$) was associated with an increase in MACEs (Table 4).

Fig. 2 illustrates the Kaplan–Meier curves for MACE-free survival (log-rank $p = 0.031$) in patients divided according to the tertiles of VLF power (< 3.75 , $3.75\text{--}4.61$, $> 4.61 \ln \text{ms}^2$). Patients within tertile 1 of VLF power had the lowest MACE-free survival probability.

Predictors of hospitalization

A total of 98 hospitalizations were recorded during the follow-up period. The causes of hospitalization included CV events ($n = 25$), gastrointestinal disorders or bleeding ($n = 11$), infectious diseases or sepsis ($n = 33$), malignancy ($n = 15$), musculoskeletal disorders or fractures ($n = 6$), complications of arteriovenous access ($n = 3$), and others ($n = 5$).

Table 4. Predictors for MACEs in univariate and multivariate analysis using Cox proportional hazards model

Parameter	Univariate		Multivariate (forward)	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (per 1 year)	1.021 (0.992–1.051)	0.159	–	–
Gender (men vs. women)	1.325 (0.689–2.548)	0.399	–	–
Current smoker	3.177 (1.122–8.997)	0.030	–	–
Dialysis vintage (per 1 year)	0.990 (0.928–1.056)	0.990	–	–
Diabetes mellitus	2.055 (1.051–4.017)	0.035	–	–
Hypertension	2.353 (1.072–5.163)	0.033	–	–
Congestive heart failure	1.448 (0.713–2.944)	0.306	–	–
Coronary artery disease	2.410 (1.248–4.653)	0.009	2.047 (1.034–4.052)	0.040
Cerebrovascular disease	2.541 (1.224–5.276)	0.012	–	–
Systolic BP before dialysis (per 1 mmHg)	1.014 (1.002–1.026)	0.021	–	–
Diastolic BP before dialysis (per 1 mmHg)	1.011 (0.989–1.034)	0.329	–	–
Ultrafiltration rate (per 1 %)	1.475 (1.161–1.873)	0.001	1.543 (1.204–1.978)	0.001
Laboratory parameters				
Albumin (per 1 g/dL)	0.410 (0.148–1.137)	0.087	–	–
Fasting glucose (per 1 mg/dL)	1.009 (1.004–1.014)	< 0.001	–	–
Triglycerides (per 1 mg/dL)	2.065 (0.554–7.696)	0.280	–	–
Total cholesterol (per 1 mg/dL)	1.001 (0.993–1.009)	0.869	–	–
HDL-C (per 1 mg/dL)	0.980 (0.949–1.012)	0.225	–	–
LDL-C (per 1 mg/dL)	0.995 (0.985–1.006)	0.361	–	–
Hemoglobin (per 1 g/dL)	1.081 (0.805–1.453)	0.604	–	–
hs-CRP (per log mg/L)	1.381 (0.754–2.530)	0.296	–	–
Creatinine (per 1 mg/dL)	0.986 (0.854–1.150)	0.858	–	–
Potassium (per 1 mmol/L)	1.051 (0.683–1.617)	0.821	–	–
Total calcium (per 1 mg/dL)	1.305 (0.951–1.791)	0.099	–	–
Phosphorus (per 1 mg/dL)	1.337 (0.973–1.835)	0.073	–	–
Calcium-phosphorus product (per 1 mg ² /dL ²)	1.037 (1.007–1.067)	0.015	–	–
iPTH (per log pg/mL)	1.279 (0.558–2.930)	0.560	–	–
Kt/V (per 1 Daugirdas)	0.329 (0.082–1.315)	0.116	–	–
Medications (users vs. non-users)				
ACE inhibitors or ARBs	2.963 (1.481–5.929)	0.002	2.960 (1.291–6.786)	0.010
Beta-blockers	3.006 (1.522–5.939)	0.002	2.215 (1.021–4.808)	0.044
Calcium channel blockers	1.840 (0.905–3.741)	0.092	–	–
Statins	1.645 (0.774–3.499)	0.196	–	–
HRV parameters (frequency domain)				
VLF (per ln ms ²)	0.785 (0.681–0.905)	0.001	0.727 (0.624–0.848)	< 0.001
LF (per ln ms ²)	0.963 (0.906–1.023)	0.219	–	–
HF (per ln ms ²)	0.975 (0.919–1.035)	0.408	–	–
LF/HF ratio	0.877 (0.667–1.153)	0.348	–	–

Values expressed as hazard ratios (HR) and 95% confidence interval (CI). Abbreviations are the same as in Table 1

Fig. 2. Kaplan-Meier curves for MACE-free survival (log-rank $p = 0.031$) in patients divided according to the tertiles of VLF power (< 3.75, 3.75–4.61, > 4.61 ln ms²). Patients within tertile 1 of VLF power had the lowest MACE-free survival probability.

In multivariate forward Cox proportional hazards model, low serum albumin levels (HR, 0.314; 95% CI, 0.139–0.709; $p = 0.005$), low serum creatinine levels (HR, 0.880; 95% CI, 0.782–0.991,

Table 5. Predictors for hospitalization in univariate and multivariate analysis using Cox proportional hazards model

Parameter	Univariate		Multivariate (forward)	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (per 1 year)	1.005 (0.987–1.024)	0.570	–	–
Gender (men vs. women)	1.186 (0.797–1.763)	0.401	–	–
Current smoker	1.045 (0.425–2.570)	0.924	–	–
Dialysis vintage (per 1 year)	0.998 (0.960–1.037)	0.910	–	–
Diabetes mellitus	1.307 (0.880–1.943)	0.185	–	–
Hypertension	1.011 (0.674–1.519)	0.956	–	–
Congestive heart failure	1.317 (0.845–2.052)	0.224	–	–
Coronary artery disease	1.263 (0.821–1.941)	0.288	–	–
Cerebrovascular disease	1.387 (0.822–2.341)	0.221	–	–
Systolic BP before dialysis (per 1 mmHg)	1.006 (0.999–1.014)	0.090	–	–
Diastolic BP before dialysis (per 1 mmHg)	1.014 (1.000–1.028)	0.049	–	–
Ultrafiltration rate (per 1 %)	1.143 (0.990–1.319)	0.068	–	–
Laboratory parameters				
Albumin (per 1 g/dL)	0.295 (0.157–0.555)	< 0.001	0.314 (0.139–0.709)	0.005
Fasting glucose (per 1 mg/dL)	1.005 (1.002–1.008)	0.004	–	–
Triglycerides (per 1 mg/dL)	2.319 (0.989–5.421)	0.053	–	–
Total cholesterol (per 1 mg/dL)	1.001 (0.996–1.006)	0.809	–	–
HDL-C (per 1 mg/dL)	0.985 (0.967–1.004)	0.129	–	–
LDL-C (per 1 mg/dL)	0.998 (0.991–1.004)	0.509	–	–
Hemoglobin (per 1 g/dL)	1.038 (0.859–1.255)	0.701	–	–
hs-CRP (per log mg/L)	1.726 (1.200–2.484)	0.003	–	–
Creatinine (per 1 mg/dL)	0.909 (0.828–0.998)	0.044	0.880 (0.782–0.991)	0.034
Potassium (per 1 mmol/L)	0.746 (0.557–1.001)	0.051	–	–
Total calcium (per 1 mg/dL)	1.066 (0.875–1.298)	0.526	–	–
Phosphorus (per 1 mg/dL)	1.218 (1.008–1.473)	0.042	–	–
Calcium-phosphorus product (per 1 mg ² /dL ²)	1.019 (1.001–1.038)	0.035	1.027 (1.009–1.045)	0.003
iPTH (per log pg/mL)	1.080 (0.674–1.732)	0.749	–	–
Kt/V (per 1 Daugirdas)	0.385 (0.171–0.868)	0.021	0.245 (0.091–0.656)	0.005
Medications (users vs. non-users)				
ACE inhibitors or ARB	0.754 (0.428–1.329)	0.329	–	–
Beta-blockers	1.224 (0.742–2.021)	0.429	–	–
Calcium channel blockers	0.896 (0.537–1.494)	0.673	–	–
Statins	0.862 (0.504–1.472)	0.586	–	–
HRV parameters (frequency domain)				
VLF (per ln ms ²)	0.861 (0.778–0.954)	0.004	0.873 (0.785–0.971)	0.012
LF (per ln ms ²)	0.980 (0.933–1.030)	0.429	–	–
HF (per ln ms ²)	0.993 (0.945–1.043)	0.767	–	–
LF/HF ratio	0.900 (0.764–1.061)	0.209	–	–

Values expressed as hazard ratios (HR) and 95% confidence interval (CI). Abbreviations are the same as in Table 1

$p = 0.034$), high serum calcium-phosphorus product levels (HR, 1.027; 95% CI, 1.009–1.045; $p = 0.003$), and low Kt/V values (HR, 0.245; 95% CI, 0.091–0.656, $p = 0.005$) were all associated with hospitalization. Low VLF power (HR, 0.873; 95% CI, 0.785–0.971; $p = 0.012$) was an independent predictor of hospitalization after we controlled for other risk factors (Table 5).

Fig. 3 presents the Kaplan–Meier curves for hospitalization-free survival (log-rank $p = 0.012$) in patients divided according to the tertiles of VLF power (< 3.75, 3.75–4.61, > 4.61 ln ms²). Patients within tertile 1 of VLF power had the lowest hospitalization-free survival probability.

Discussion

In this prospective cohort study, we investigated the link between HRV and the risk of MACEs and hospitalization in chronic HD patients over an observation period of nearly 3 years. Our findings showed that reduced HRV based on 5-minute ECG recordings was useful in predicting adverse outcomes. In ESRD patients with maintenance HD, decreased VLF

Fig. 3. Kaplan–Meier curves for hospitalization-free survival (log-rank $p = 0.012$) in patients divided according to the tertiles of VLF power (< 3.75 , 3.75 – 4.61 , > 4.61 ln ms²). Patients within tertile 1 of VLF power had the lowest hospitalization-free survival probability.

power was an independent predictor of MACEs and hospitalization.

The control of periodic fluctuations in heart rates in response to extracardiac factors is mediated by impulses from the autonomic nervous system. Functionally efficient autonomic cardiovascular control indicates higher values of HRV. In chronic HD patients, HRV is drastically decreased, suggesting enhanced sympathetic activation and autonomic dysfunction, when compared with those of healthy individuals [16]. In clinical settings, reduced HRV has been shown to predict death in patients with ESRD [10, 11]. Although the relationship between deficits in autonomic control and death remains complex, accumulating evidence indicates that blunted vagal activity might play a key role in sympathovagal imbalance, aiding hypertension, myocardial hypertrophy and fibrosis in CKD [17].

A novel crucial finding of the present study is that a decrease in VLF power independently predicts MACEs and hospitalization in chronic HD patients. Compared with other power spectrum components of HRV, the physiologic implications of VLF are less clear. VLF power is deemed to reflect vasomotor function, the renin-angiotensin-aldosterone system (RAAS), and/or parasympathetic influence [18, 19]. Although the role of VLF power is physiologically obscure, reduced VLF power has been reported as a powerful predictor of ventricular tachycardia in patients with prior myocardial infarction [20], and CV events in heart failure patients [21]. In accordance with our results, Chandra et al. [22] indicated that lower VLF power is significantly associated with higher risk of CV events in non-dialysis patients with CKD stages 3–5. Although low HRV are linked with increased risk of unfavorable prognosis, accumulating evidence indicates that VLF power has stronger associations with adverse outcomes than LF, HF, and the LF/HF ratio [8, 23–24]. In Framingham Heart Study, frequency-domain HRV measures except the LF/HF ratio were associated with risk for CV events [23]. It is probably because the LF/HF ratio may not accurately quantify cardiac sympatho-vagal balance [25]. Reduced VLF power may reflect the blunt cardiac response toward external stress [26]. The association of decreased VLF power with MACEs and hospitalization might be partly attributable to autonomic and vasomotor dysfunction reflected by reduced VLF power in HRV. Longenecker et al. [27] demonstrated a strong correlation between low HRV and atherosclerotic disease independent of cardiac systolic function among 108 chronic HD patients. This suggests that impaired cardiac autonomic modulation might be closely linked to the process of atherosclerosis and subsequent MACEs or hospitalization in this patient population.

Furthermore, decreased VLF power is associated with depression and decreased physical activity [26, 28–29], which may play roles in enhancing the development of cardiac

events in these vulnerable patients. Potential mechanisms might include procoagulant and proinflammatory processes mediating cardiac morbidity and mortality in high-risk populations [30]. The inverse association between HRV and inflammation markers has been demonstrated in patients with heart failure and coronary heart disease [31-33]. Lampert et al. [34] demonstrated that decreased HRV, including VLF power, is associated with increased levels of C-reactive protein. Taken together, these studies have supported the evidence of vagal anti-inflammatory effects [35]. Thus, autonomic dysfunction might lead to inflammation, representing another plausible pathway of increased development of MACEs and hospitalization.

In our study, we found that patients receiving ACE inhibitors or ARBs and those with use of beta-blockers had a higher risk of MACEs. In an observational study, RAAS blockades were associated with a reduction in left ventricular mass in maintenance HD patients [36]. However, this improvement in the surrogate marker does not inevitably translate to a decreased risk of adverse outcomes. A recent meta-analysis showed that dialysis patients with ACE inhibitors or ARBs treatment did not have a significantly reduced risk of CV events compared with controls [37]. Furthermore, Wu et al. [38] reported that users of ACE inhibitors or ARBs had an increased risk of CV events in 30,364 dialysis patients during a median follow-up period of 3.9 years. In particular, CV events were more common in patients who used ACE inhibitors or ARBs for a short duration. In our study, VLF power did not differ between users and non-users of ACE inhibitors or ARBs and beta-blockers. But these medications were more likely to be applied to severely ill patients, such as those with congestive heart failure and hypertension. Nevertheless, this study was not a clinical trial aimed at investigating the effects of medication, and the data on cumulative exposure duration and defined daily dose were lacking. We supposed that selection bias might explain the positive associations in use of RAAS blockades and beta-blockers with MACEs in the present study.

As stated, the major causes of hospitalization in the present study were CV events and infection. We showed that the serum calcium-phosphorus product level was an independent predictor of hospitalization. Abnormal mineral metabolism is common among patients with ESRD and is associated with morbidity and mortality in such patients [39]. In accordance with our findings, Block et al. [40] reported a significantly increased risk of all-cause hospitalization in chronic HD patients with higher levels of serum calcium-phosphorus product. The mechanisms underlying increased risk of hospitalization associated with disturbances of mineral metabolism remain uncertain. Accumulating evidence indicates that elevated levels of serum calcium-phosphorus product and disorders of calcium homeostasis may accelerate vascular calcification and induce inflammation [41, 42]. Moreover, a recent study showed that higher dialysate calcium concentration is associated with increased sympathetic activity during HD, which might lead to unfavorable outcomes [43].

Our study had several limitations. First, the patient number of this prospective cohort study is relatively small and the observation period might not have been adequately long. Second, we excluded patients receiving nighttime HD to attenuate the influence of circadian rhythm on HRV. However, we cannot preclude the possibility that some patients' circadian rhythm might have been impaired. A 24-hour Holter ECG for HRV analysis could offer more information on each patient and differences in HRV during a day. Third, the laboratory biomarkers as well as ECG recordings were analyzed cross-sectionally at baseline. We may know better if repeated ECG recordings and readings of biomarkers have been done during the follow-up period. Finally, there were no time-domain HRV measurements in our study. Reduced time-domain HRV can be a predictive factor in clinical settings [10]. Indeed, a good correlation ($r = 0.85$) between time-domain and frequency-domain HRV parameters has been reported previously [44]. Further studies should include both time- and frequency-domain HRV parameters for understanding the role of cardiac autonomic function in maintenance HD patients more clearly.

Conclusion

In summary, we demonstrated that reduced HRV measurements were linked to an increased risk of MACEs and hospitalization in this prospective cohort study of 179 chronic HD patients. Decreased VLF power independently predicts MACEs and hospitalization. Assessing cardiac autonomic function through HRV based on 5-minute ECG recordings is of pivotal prognostic significance in risk-stratification for maintenance HD patients.

Disclosure Statement

The authors declare no conflicts of interest.

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