


Heart rate variability is an indicator for intradialytic hypotension among chronic hemodialysis patients

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Abstract

Background Intradialytic hypotension (IDH) carries adverse impact. Heart rate variability (HRV) represents autonomic cardiac regulation which influences intradialytic blood pressure. We aimed to evaluate the association between IDH and HRV.

Methods This prospective study was carried out in a teaching hospital in Taiwan from June to August 2010. Adult patients on chronic hemodialysis without active medical conditions were enrolled and received HRV measurements for 4 times (before and during an index hemodialysis session). Patients were categorized by the changes of systolic blood pressure during the index

hemodialysis into Group 1 (elevation >20 mmHg), Group 2 (decrease >20 mmHg), and Group 3 (others). Then we compared HRV indices among the three groups, and determined the indicators for IDH.

Results One hundred and seventy-one patients (96 women, mean age 64.9 years) were enrolled and categorized into Group 1 ($n = 47$, 27.5 %), Group 2 ($n = 45$, 26.3 %) and Group 3 ($n = 79$, 46.2 %). Comparing with Group 1 and/or Group 3, Group 2 had significantly higher blood pressure at hemodialysis initiation (most $p < 0.001$) and statistically lower levels of HRV indices including variance, total power, very low-frequency, low-frequency and high-frequency since the middle phase of the hemodialysis. By logistic regression method, higher systemic blood pressure [odds ratio (OR) 1.048; $p < 0.001$], heart rate (OR 1.093; $p = 0.021$), low-frequency/high-frequency ratio (OR 1.715; $p = 0.022$), as well as lower variance (OR 0.639; $p = 0.048$) at hemodialysis initiation were independently associated with intradialytic blood pressure changes.

Conclusions HRV is a useful indicator for IDH among hemodialysis patients.

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Keywords Autonomic nervous system · Heart rate variability · Hemodialysis · Intradialytic hypotension · Sympathetic activity

Abbreviations

Gp	Group
HF	High frequency
HRV	Heart rate variability
LF	Low frequency
TP	Total power
Var	Variance of the $R-R$ interval values
VLF	Very low frequency

Introduction

Intradialytic hypotension (IDH), defined as a decrease in systolic blood pressure (SBP) of more than 20 mmHg or a decrease in mean arterial pressure (MAP) of more than 10 mmHg [1], is a common complication during hemodialysis (HD). It precludes patients from optimal ultrafiltration (UF) and clearance target, and carries adverse effects among HD patients. The mechanisms of IDH are inappropriate compensatory responses to hypovolemia, which is usually associated with impaired autonomic nervous system (ANS). ANS dysfunction is found in more than 50 % of patients on maintenance HD, and it plays an important role in IDH [2]. Among uremic patients, the ANS dysfunction is mainly resulted from the defect of baroreceptor which is responsible for the increment of circulating catecholamines and efferent sympathetic activity during hypotension. In addition, down-regulation of alpha-adrenergic receptors and inappropriately activation of Bezold–Jarisch reflex, which decreases sympathetic and increases parasympathetic nervous activities, may also contribute to IDH [3–5].

Heart rate variability (HRV), which means variation of beat-to-beat interval, is a noninvasive tool to evaluate ANS regulatory functions that control cardiovascular systems. The heart rate has a high degree of beat-to-beat variability in normal individuals, while reduced HRV is a significant risk factor for more cardiac events [6] and higher mortality including cardiac death in cardiovascular disease and healthy populations [7, 8]. HRV is usually measured by time domain analysis, e.g., the standard deviation of normal to normal interval (SDNN), or frequency domain analysis which includes several indices such as total power (TP), very low-frequency (VLF), low-frequency (LF), high-frequency (HF), and LF/HF ratio [9]. Among the frequency domain indices, VLF is thought to be influenced by the thermoregulation of vasomotor tone; LF activity is now widely recognized to reflect a mixture of both the sympathetic and parasympathetic tone; HF activity has been linked to parasympathetic nervous activity, which is associated with the vagal-mediated modulation of heart rate; LF/HF ratio is an index of sympathovagal balance and thus of autonomic status or sympathetic nervous activities; whereas TP can be estimated with the sum of the frequencies [9–13]. As to the time domain indices, SDNN is the square root of “variance of the R - R interval values (variance)” which is mathematically equal to TP of spectral analysis. Thus, SDNN and variance reflect all the cyclic components responsible for variability in the period of recording [9, 14].

Most of the previous studies evaluating the association between HRV indices and hemodynamic status during HD

enrolled small number of participants (around 9–56 patients) and only applied certain indices (LF, HF, LF/HF, and SDNN) [5, 11, 15–17]. Besides, the main findings of these studies were diverse [18]. For example, some studies reported that LF/HF ratio increased in uneventful HD and decreased in patients with IDH [5, 11, 15, 16], while another study found that LF/HF ratio contrarily increased associated with hypotension-prone response among HD patients [19]. These discordant findings make the role of HRV indices inconclusive, and we also proposed a hypothesis that some HRV indices besides LF/HF ratio may play certain roles in the occurrence of IDH. Therefore, we conducted a study with larger number of participants to investigate the association between HRV indices and intradialytic blood pressure (BP), and to determine the indicators for IDH.

Materials and methods

Study design and populations

This prospective study was carried out in a teaching hospital in Northern Taiwan, which was approved by the Institutional Review Board of Saint Mary Hospital Luodong. Written informed consents were obtained from all participants, and the data were analyzed anonymously.

Patients were eligible for enrollment if they were adults who underwent maintenance HD with stable conditions during the period from June to August 2010. Exclusion criteria included patients who were less than 18 years of age, who initiated HD for less than 3 months, who had arrhythmia or active infection, or who were not willing to receive HRV measurement. Enrolled patients were arranged to receive HRV measurements before HD (HRV-0) and three times during HD (HRV-1, -2, and -3 at initial, middle, and late phases of the index HD session, respectively). Besides, patients' BP was repeatedly checked at initiation of HD (BP-1) and every 30 min throughout the HD session. All participants were categorized into three groups according to the SBP changes during HD, which were defined by both (1) increased (or decreased) SBP at the end of HD comparing to that in the beginning, and (2) the difference between the SBP at end of HD and the measured lowest (or highest) SBP >20 mmHg or not. In more detail, the participants who had an elevated SBP at the end of HD comparing to BP-1, with a difference of SBP >20 mmHg between the latest SBP and the lowest SBP during the HD session were categorized into Group 1. While patients who had a decreased SBP at the end of HD with a difference of SBP >20 mmHg between the latest SBP and the highest SBP were categorized into Group 2.

Other participants who did not meet the criteria of Groups 1 and 2 were categorized into Group 3.

The baseline demographic data, comorbid diseases, etiologies of uremia, and medications were documented from patients' medical records and/or relevant clinical and imaging examinations. Diabetes mellitus was defined as undergoing oral antidiabetic drugs or insulin therapy, or glycosylated hemoglobin $\geq 6.5\%$ in untreated patients. Hypertension was defined as taking antihypertensive agents, or those who do not take antihypertensive pills but have a pre-dialysis BP of higher than 140/90 mmHg in more than half of the records within the recent 1 month [1]. Hypotension was defined by a SBP of less than 100 mmHg in the interdialytic period [20]. Heart failure was defined by class III/IV of New York Heart Association Functional Classification.

The clinical parameters included blood tests such as complete blood cell count, blood urea nitrogen, serum creatinine, calcium, phosphate, albumin, sodium, potassium, sugar, glycosylated hemoglobin, intact-parathyroid hormone, and lipid profiles, as well as cardiothoracic ratio were recorded at the time of HRV measurement. Besides, the calcium and sodium concentration of dialysate was also documented. Then we compared the differences of demographic and clinical parameters among the three groups, and tried to evaluate the role of HRV indices in the process of IDH.

Measurements of heart rate variability

HRVs were measured using an analyzer (SSIC, Enjoy Research Inc., Taiwan). It took 5 min while the patients lay quietly with normal breath for more than 20 min. Under a sampling rate of 512 Hz, signals from a lead I electrocardiogram were documented by an 8-bit analog-to-digital converter. Stationary R - R values were resampled and interpolated to produce the continuity in the time domain, and resulted in the data of variance. Fast Fourier transformation was utilized to perform power spectral analysis which quantified power spectrum into the standard frequency-domain measurements including VLF (0.003–0.04 Hz), LF (0.04–0.15 Hz), HF (0.15–0.40 Hz), TP (≤ 0.40 Hz), and LF/HF ratio [9]. These indices were logarithmically transformed to correct their skewed distributions [21].

Statistical analysis

Statistical analyses were performed using the Scientific Package for Social Science (PASW Statistics for Windows, Version 18.0, Chicago: SPSS Inc). Chi square test with Yate's correction was used for comparing the categorical variables among the three groups. Two-way analysis of

variance (ANOVA) were performed to compare the differences in continuous variables with different intradialytic BP changes (Groups 1, 2, 3) and at different time points (initial, middle, and late phases of the HD), while Post hoc multiple comparison with Bonferroni method for equal variances assumption were further undertaken for group-to-group analysis. Paired student's t test was used to compare the values of individual HRV indices at different phases of the HD in each group. Microsoft Office Excel 2013 was used to draw the plots comparing HRV indices among groups. Continuous data were expressed as mean \pm standard deviation, whereas categorical variables were shown as number (percentage) unless otherwise specified.

Then we analyzed the independent indicators for IDH by using backward likelihood ratio selection method of logistic regression analysis. All the variables were selected for multivariate analysis if they had a $p \leq 0.15$ on univariate analysis. The basic model-fitting techniques for variable selection, goodness-of-fit assessment, and regression diagnostics were used in our regression analyses to ensure the quality of analysis results. Specifically, we used the stepwise variable selection procedure with both significance level for entry and significance level for stay set to 0.10 or larger to select the relevant covariates into the final Logistic regression analysis. In all statistical analyses, two-sided $p \leq 0.05$ was considered statistically significant.

Results

During the study period from June to August 2010, 202 patients who had received HD for more than 3 months were screened. After excluding 7 patients with infectious disease, 14 patients with obvious arrhythmia, and 10 patients who hesitated to receive HRV measurement, a total of 171 patients (96 women, mean age 64.9 ± 12.9 years) were enrolled and categorized into Group 1 ($n = 47, 27.5\%$), Group 2 ($n = 45, 26.3\%$) and Group 3 ($n = 79, 46.2\%$).

Comparisons of demographic and clinical data

In the comparisons of demographic data and comorbid diseases including diabetes, hypertension and heart failure, along with baseline clinical and laboratory parameters, only "underlying hypotension" was significantly different among the three groups ($p = 0.001$). However, the post hoc comparison did not reveal significance of this variable between any two groups.

In the clinical parameters at the index HD, which included dry weight, %UF (UF divided by body weight), hemodynamics, as well as sodium and calcium concentration in dialysate, only the initial hemodynamics

including SBP-1, diastolic BP (DBP)-1, MAP-1, and proportion of BP-1 \geq 130/85 mmHg were of significant differences among the three groups. Whereas Group 2 was found to have significantly higher SBP-1, DBP-1 and MAP-1 comparing with either Group 1 or Group 3 (all $p < 0.001$ except Group 1 comparing with Group 2 in DBP-1 whose $p = 0.002$) (Supplementary Table 1).

Comparisons of HRV indices

Two-way ANOVA revealed significant differences in continuous variables among the three groups ($F = 3.008$; $p < 0.001$), but not in the time-dependent changes ($F = 1.326$; $p = 0.122$). Besides, the interactions among the two above-mentioned factors were excluded owing to lack of significant difference ($F = 0.802$; $p = 0.849$).

In the three-group comparison, the heart rate (HR) at initial (HR-1, $p = 0.016$), middle (HR-2, $p = 0.027$), and late phase (HR-3, $p = 0.049$) of HD were all significantly different. In further two-groups comparison, the Group 2 had a statistically higher HR-1 than that in Group 1 ($p = 0.017$) and a higher HR-2 than that in Group 3 ($p = 0.025$) (Supplementary Table 1).

In Fig. 1, the three groups presented three uncrossed lines with stepwise decreased values by the order of Group 1, Group 3, to Group 2 throughout the entire HD session (HRV-1 to HRV-3) in variance, VLF, LV, HF, and TP. Statistically, the differences in these HRV indices comparisons were not yet reached significance at baseline (HRV-0) and initial phase (HRV-1), but progressed to be significant at middle (HRV-2) and late phases (HRV-3) of HD. Most of the above indices at HRV-2 and HRV-3 were of significant difference in the inter-group analyses, whereas the post hoc comparison disclosed that the indices in Group 2 were significantly lower than Group 1 and/or Group 3. Differently, the order of decreasing values of LF/HF ratio changed to be Group 2, Group 1, to Group 3. And the LF/HF ratio in Group 2 were significantly higher than that in Group 3 at HRV-2 ($p = 0.046$). As to the longitudinal change of HRV indices in each group, all indices in Group 1 increased from HRV-1 to HRV-2 (statistically significant in LF, HF, TP, and variance), but decreased in the later phase of HD (from HRV-2 to HRV-3). In the contrary, most of the HRV indices except LF/HF ratio in Group 2 went downward gradually throughout the entire HD (HRV-1 to HRV-3) although they did not yet reach statistical significances (Supplementary Table 1; Fig. 1).

To determine the effect of baseline BP on intradialytic BP change, we used a baseline BP of 130/85 mmHg (SBP served as the priority criteria in cases whose SBP and DBP did not indicate the same side) to stratify Groups 1 and 2

into four groups, namely, Group 1 with baseline BP $<$ 130/85 mmHg [Gp1(L), $n = 11$], Group 1 with baseline BP \geq 130/85 mmHg [Gp1(H), $n = 36$], Group 2 with baseline BP $<$ 130/85 mmHg [Gp2(L), $n = 28$], and Group 2 with baseline BP \geq 130/85 mmHg [Gp2(H), $n = 17$]. The values of most of the HRV indices (except LF/HF ratio) were consistently lower in Group 2 than in Group 1 regardless of their baseline BP. Besides, in both Groups 1 and 2, the HRV values in higher baseline BP subgroup were lower than that in lower BP subgroup. However, the differences between the two subgroups were not statistical significant within the same group (Fig. 1).

Independent indicators of intradialytic hypotension

Then we compared patients with IDH (Group 2) to those without (Groups 1 and 3) to investigate the independent indicators for IDH by using logistic regression method. The variables including gender, age, diabetes mellitus, heart failure, cardiothoracic ratio, %UF, SBP-1, DBP-1, HR-1, variance-1, TP-1, LF-1, HF-1, LF/HF ratio-1, along with laboratory examinations in serum (hemoglobin, albumin, blood urea nitrogen, creatinine, sodium, potassium, calcium, phosphate) and dialysate (calcium and sodium) were screened. The variables with $p \geq 0.15$ in univariate analyses were further put into the final multivariate model for analysis. These variable included age, diabetes mellitus, heart failure, SBP-1, DBP-1, HR-1, variance-1, TP-1, LF-1, HF-1, LF/HF ratio-1, serum creatinine value, and dialysate calcium concentration. VLF was excluded from the multivariate analysis because it is considered a dubious measurement and suggested to be avoided in the short-term (≤ 5 min) HRV interpretation [9].

We found that higher SBP-1 [odds ratio (OR) 1.048; 95 % confidence interval (CI) 1.027–1.070, $p < 0.001$], HR-1 (OR 1.093; 95 % CI 1.013–1.179, $p = 0.021$), LF/HF ratio-1 (OR 1.715; 95 % CI 1.080–2.724, $p = 0.022$), as well as lower variance-1 (OR 0.639; 95 % CI 0.411–0.995, $p = 0.048$) were independent indicators for IDH (Table 2).

Discussion

Although several previous studies had tried to evaluate the association between HRV indices and intradialytic hemodynamic status, the results were diverse and inclusive [5, 11, 15, 16, 19, 22, 23]. To the best of our knowledge, the current study is the largest one addressing this issue, and it is among the few studies using multivariate analysis to determine the independent indicators for IDH [16]. Most

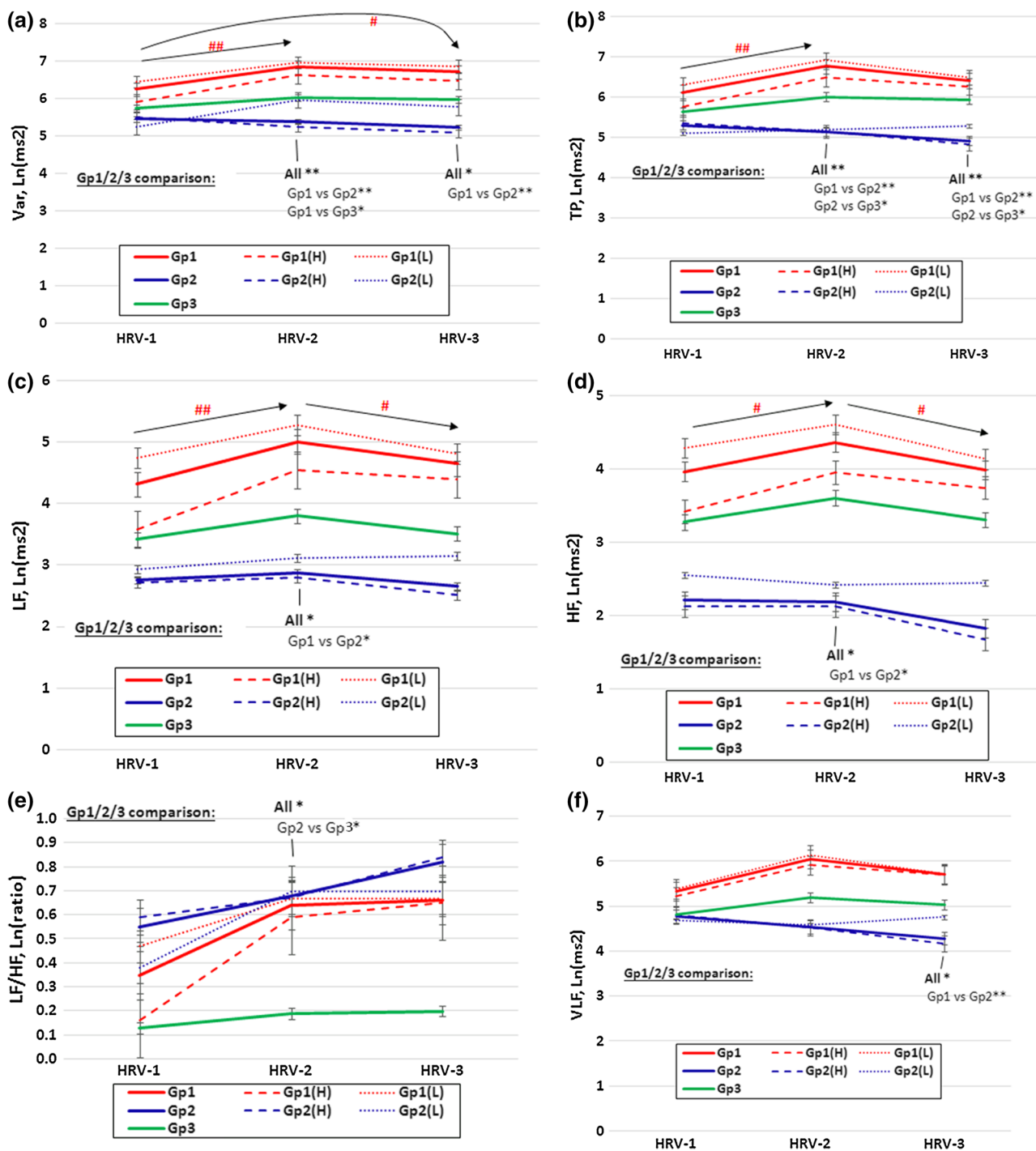


Fig. 1 Plots comparing HRV indices among the three groups. The indices included Var (a), TP (b), LF (c), HF (d), LF/HF ratio (e), and VLF (f). Red solid line Group 1 ($n = 47$); blue solid line Group 2 ($n = 45$); green solid line Group 3 ($n = 79$). Red dashed line Gp1(H), Group 1 with baseline blood pressure $\geq 130/85$ mmHg ($n = 36$); red dotted line Gp1(L), Group 1 with baseline blood pressure $<130/85$ mmHg ($n = 11$); blue dashed line Gp2(H), Group 2 with baseline blood pressure $\geq 130/85$ mmHg ($n = 17$); blue dotted line Gp2(L), Group 2 with baseline blood pressure $<130/85$ mmHg

($n = 28$). HRV-1, -2, and -3 were HRV measured at initial, middle, and late phases of the index hemodialysis session, respectively. “All” denotes the inter-group significance evaluated using three-way analysis of variance (ANOVA), whereas post hoc test were applied for further group-to-group analysis. * $p \leq 0.05$; ** $p \leq 0.001$ as comparing among (or between) groups at the same hemodialysis phase. # $p \leq 0.05$; ## $p \leq 0.001$ as comparing the same HRV indices values between different hemodialysis phases (color figure online)

Table 1 Comparisons of demographic data among the three groups

Covariate	Group 1 SBP [↑] >20 mmHg (n = 47)	Group 2 SBP [↓] >20 mmHg (n = 45)	Group 3 others (n = 79)	Inter- group p value	Post hoc multiple comparison (p value)
Age (years)	65.6 ± 14.0	61.7 ± 12.6	66.4 ± 12.2	0.135	NS
Gender (woman)	27 (57.4)	25 (55.6)	44 (55.7)	0.860	–
Comorbidities					
Diabetes mellitus	14 (29.8)	23 (51.1)	26 (32.9)	0.968	–
Hypertension	37 (78.7)	31 (68.9)	56 (70.9)	0.391	–
Taking antihypertensive agents	35 (74.5)	28 (62.2)	50 (63.3)	0.359	–
Taking beta-blockers or ACEi/ARB	19 (40.4)	14 (31.1)	21 (26.6)	0.113	–
Taking alfa-blockers	7 (14.9)	6(13.3)	12 (15.2)	0.601	–
Taking beta-blockers	13 (27.7)	6 (13.3)	14 (17.7)	0.189	–
Taking CCB	23 (48.9)	22 (48.9)	32 (40.5)	0.402	–
Taking diuretics	5 (10.6)	6 (13.3)	9 (11.4)	0.916	–
Taking ACEi + ARB	8 (17.0)	9 (20.0)	11 (13.9)	0.483	–
Hypotension	2 (4.3)	6 (13.3)	21 (26.6)	0.001	–
Taking midodrine	1 (2.1)	2 (4.4)	10 (12.7)	0.024	–
Heart failure	15 (31.9)	7 (15.6)	19 (24.1)	0.434	–
Coronary artery disease	16 (34.0)	10 (22.2)	16 (20.3)	0.097	–
Cerebrovascular disease	8 (17.0)	6 (13.3)	9 (11.4)	0.378	–
Peripheral arterial disease	4 (8.5)	3 (6.7)	6 (7.6)	0.882	–
Liver cirrhosis	3 (6.4)	3 (6.7)	9 (11.4)	0.266	–
Malignancy	3 (6.4)	2 (4.4)	13 (16.5)	0.062	–
Causes of uremia				0.394	–
Diabetic nephropathy	12 (25.5)	20 (44.4)	22 (27.8)		
Hypertension	0 (0)	1 (2.2)	1 (1.3)		
Chronic GN	27 (57.4)	19 (42.2)	43 (54.4)		
PCKD	2 (4.3)	2 (4.4)	7 (8.9)		
Others	6 (12.8)	3 (6.7)	6 (7.6)		
Baseline data					
Cardio-thoracic ratio (%)	52.1 ± 6.0	51.0 ± 4.8	51.8 ± 4.7	0.576	NS
Blood urea nitrogen (mg/dL)	74.5 ± 22.2	74.5 ± 17.8	75.2 ± 20.2	0.977	NS
Creatinine (mg/dL)	10.3 ± 2.4	11.4 ± 5.6	10.3 ± 2.2	0.192	NS
Kt/V	1.45 ± 0.25	1.43 ± 0.21	1.42 ± 0.25	0.771	NS
Urea reduction ratio (%)	75.8 ± 5.7	90.1 ± 107.1	73.3 ± 9.9	0.248	NS
Calcium (mg/dL)	9.0 ± 0.9	9.0 ± 0.7	9.1 ± 0.7	0.776	NS
Phosphate (mg/dL)	4.7 ± 1.9	5.2 ± 1.7	4.9 ± 1.6	0.406	NS
Calcium × phosphate (mg/dL) ²	42.4 ± 17.1	46.5 ± 14.8	44.8 ± 15.6	0.460	NS
Albumin (g/dL)	3.80 ± 0.33	3.80 ± 0.32	3.78 ± 0.34	0.915	NS
Potassium (mEq/L)	4.7 ± 0.7	4.8 ± 0.8	4.6 ± 0.8	0.592	NS
Sodium (mEq/L)	137.0 ± 2.9	135.0 ± 18.9	138.0 ± 3.2	0.265	NS
i-PTH (µg/L)	281.5 ± 362.5	239.3 ± 320.9	324.9 ± 612.9	0.637	NS
Hemoglobin (g/dL)	9.9 ± 1.3	9.6 ± 1.3	9.7 ± 1.5	0.565	NS
Hematocrit (%)	30.6 ± 3.9	29.7 ± 4.1	30.2 ± 4.6	0.565	NS
White blood cell (×10 ⁹ /L)	6.09 ± 2.07	6.21 ± 1.79	6.43 ± 2.30	0.667	NS
Total cholesterol (mg/dL)	169.0 ± 33.4	155.8 ± 30.5	162.8 ± 38.8	0.207	NS
Triglyceride (mg/dL)	158.9 ± 141.5	180.8 ± 161.7	140.1 ± 100.7	0.248	NS
Low-density lipoprotein (mg/dL)	101.9 ± 29.3	94.2 ± 28.8	97.8 ± 32.0	0.476	NS
High-density lipoprotein (mg/dL)	36.7 ± 18.6	31.9 ± 15.6	37.4 ± 20.2	0.265	NS
Sugar (postprandial) (mg/dL)	146.1 ± 47.5	158.2 ± 60.1	142.3 ± 55.8	0.295	NS

Table 1 continued

Covariate	Group 1 SBP↑ >20 mmHg (n = 47)	Group 2 SBP↓ >20 mmHg (n = 45)	Group 3 others (n = 79)	Inter- group p value	Post hoc multiple comparison (p value)
Glycated hemoglobin (%)	6.8 ± 1.2 (n = 14)	7.6 ± 1.4 (n = 24)	6.8 ± 1.6 (n = 25)	0.133	NS
At the index hemodialysis					
Dialysate sodium (mEq/L)	140.5 ± 1.3	140.3 ± 1.1	140.6 ± 1.6	0.406	NS
Dialysate calcium (mEq/L)	2.9 ± 0.3	2.8 ± 0.3	2.9 ± 0.3	0.062	NS
Dry weight (kg)	54.4 ± 11.2	64.5 ± 55.1	56.0 ± 10.6	0.204	NS
Actual UF (kg)	2.14 ± 0.91	2.30 ± 1.02	2.27 ± 0.93	0.670	NS
%UF (%)	3.94 ± 1.56	4.07 ± 1.83	4.09 ± 1.62	0.877	NS
%UF ≥ 5%	9 (19.1)	15 (33.3)	21 (26.6)	0.207	–
BP-1 ≥ 130/85 mmHg	18 (38.3)	35 (77.8)	39 (49.4)	<0.001	–

Values are presented as mean ± standard deviation or number (percentage) unless otherwise stated. *p* value was calculated using Chi square test with Yate's correction and three-way analysis of variance (ANOVA) with post hoc multiple comparison

Baseline laboratory data were the pre-dialysis data obtained when patients receiving HRV measurement

ACEi angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BP* blood pressure, *CCB* calcium-channel blocker, *GN* glomerulonephritis, *i-PTH* intactparathyroid hormone, *MAP* mean arterial pressure, *NS* not significant, *PCKD* polycystic kidney disease, *UF* ultrafiltration; %*UF* ultrafiltration divided by body weight

importantly, we underscore the role of total ANS activity in the process of IDH.

Autonomic nervous system and chronic kidney disease

The sympathetic nervous system responds to various stimuli and maintains human vital functions [24]. However, the diseased kidney would cause sympathetic overactivity which contributes to the progression of heart and kidney diseases [18]. Previous studies revealed sympathetic activity increases with a severity-dependent fashion since early chronic kidney disease [25]. Nonetheless, the sympathetic activity tends to decrease in patients who underwent HD for a longer period and it suggests that sympathetic nervous functions might be affected by the duration of HD [26].

Heart rate variability in chronic kidney disease

During mild sympathetic stimulation, the HRV indices (especially LF) increase. However, if the sympathetic stimulation is intense or prolonged, an overall decrease in HRV without correlation with the reduction in sympathetic activity would be seen [27]. The HRV indices in patients with chronic kidney disease are lower compared with healthy individuals [28]. Whereas the diminished HRV indices represent cardiovascular ANS impairment and is an independent predictor for the subsequent development of chronic kidney disease [29].

Independent indicators for intradialytic hypotension

In current study, the patients with IDH (Group 2) had the lowest values, while those with intradialytic BP elevation (Group 1) had the highest values of most HRV indices (except LF/HF ratio) which represent sympathetic, parasympathetic, or total tones. In patients without IDH (Groups 1 and 3), these HRV indices tended to increase initially when the patients facing stress (HD with UF), but decrease in the later phase of HD when the stress increased gradually. Nonetheless, this response of initial increase of HRV was lost in patients with IDH (Group 2). Finally, lower variance as well as higher LF/HF ratio, HR, and SBP at initiation of HD were proven as independent indicators for IDH (Table 2, Supplementary Table 1; Fig. 1).

Theoretically, IDH at least partially resulted from inadequate sympathetic nervous activities. While applying HRV measurement on this issue, the previous studies revealed discordant results in which LF/HF ratios were disclosed to be decreased [5, 11, 15, 16], or contrarily increased [19] during the HD session in patients with IDH. In current study, the characteristics of the patients with IDH (Group 2) consisted with chronic sympathetic nervous system overactivity which was represented by increased LF/HF ratio with decreased values of other HRV indices, increased HR, elevated BP, and suppressed baroreflex function resulting in increased BP variability [18]. During the entire HD process, the plots of LF/HF ratio in both Groups 1 and 2 went upward. However, different from the plot of Group 1 which consisted of both increased LF and

Table 2 Independent indicators for IDH measured using logistic regression (backward likelihood ratio)

Univariate analysis					Multivariate analysis				
Covariate	Standard error	<i>p</i> value	Odds ratio	95 % confidence interval	Covariate	Standard error	<i>p</i> value	Odds ratio	95 % confidence interval
SBP-1 ^a	0.009	<0.001	1.042	1.023–1.061	SBP-1 ^a	0.011	<0.001	1.048	1.027–1.070
HR-1 ^a	0.030	0.016	1.076	1.014–1.142	HR-1 ^a	0.039	0.021	1.093	1.013–1.179
Var-1 ^a	0.106	0.104	0.841	0.683–1.036	Var-1 ^a	0.226	0.048	0.639	0.411–0.995
LF/HF-1 ^a	0.151	0.116	1.268	0.943–1.704	LF/HF-1 ^a	0.236	0.022	1.715	1.080–2.724
Age ^a	0.014	0.051	0.973	0.947–1.000	–	–	–	–	–
Diabetes ^b	0.354	0.022	2.248	1.122–4.502	–	–	–	–	–
Heart failure ^b	0.458	0.128	0.498	0.203–1.222	–	–	–	–	–
DBP-1 ^a	0.022	<0.001	1.088	1.041–1.136	–	–	–	–	–
TP-1 ^a	0.097	0.118	0.859	0.710–1.039	–	–	–	–	–
HF-1 ^a	0.050	0.106	0.923	0.837–1.107	–	–	–	–	–
Creatinine (serum) ^a	0.059	0.131	1.094	0.974–1.229	–	–	–	–	–
Calcium (dialysate) ^a	0.615	0.025	0.252	0.075–0.840	–	–	–	–	–
Constant	–	–	–	–	Constant	3.462	0.001	0.000	–

Comparing Group 2 with Groups 1 + 3; variables put into multivariate analysis were selected if they had a $p \leq 0.15$ on univariate analysis. These variable included age, diabetes mellitus, heart failure, SBP-1, DBP-1, HR-1, Variance-1, TP-1, LF-1, HF-1, LF/HF-1, serum creatinine value, and dialysate calcium concentration

“–1” denotes the measurement at initial of the hemodialysis session

DBP diastolic blood pressure, HF high frequency, HR heart rate, LF low frequency, SBP systolic blood pressure, TP total power, Var variance of the R–R interval values

^a Every increment of 1 unit

^b With comparing with without

HF (more increase in LF than in HF), the plot of Group 2 was comprised of both decreased LF and HF (more decrease in HF than in LF) (Fig. 1). These changes also matched with the presentation of chronic sympathetic nervous system overactivity in which HRV would decrease, but sympathetic withdrawal with bradycardia and hypotension might occur, following a prolonged or intense stimulation [18, 27].

A decreasing HRV [30], especially which indicating a lower parasympathetic activity [31], has been established as a predictor of poor cardiac outcome, whereas increases in the variance and HF power of HRV indicating more vagotonic effect and greater cardiovascular safety [32]. Although high LF/HF ratio is often taken as an index of sympathetic overactivity which usually accompanies with hypertension, sympathetic overactivity is also commonly seen in patients with cardiovascular dysfunction which brings higher risk of IDH.

Lower variance, the reflection of lower total activities of ANS, is also an independent indicator for IDH. This finding could be explained by chronic sympathetic nervous overactivation. It also emphasized the importance of the ability of increasing both sympathetic and parasympathetic activity, rather than either one, in response to any stimulus. During HD process, those with better autonomic function may respond to the stimulus appropriately and maintain

stable intradialytic BP, whereas those with worse autonomic function may result in IDH. This phenomenon has also been described in some previous studies [5, 11].

Besides HRV indices, higher HR and BP at the initial of HD were also independent indicators of IDH. Chronic sympathetic nervous overactivity might also be an important underlying mechanism. Actually, tachycardia has been reported to be associated with lower parasympathetic activity and decreased HRV indices including LF and HF [9, 33], and either of the two situations carries higher risk of cardiovascular complications including IDH [31, 34]. There are some other possible explanations for the linkage between higher baseline SBP and IDH included: (1) higher initial SBP is probably owing to larger interdialytic weight gain which results in more intensive UF and subsequently higher risk of IDH. The UF rate might be adjusted to a less intensive degree after the occurrence of IDH resulting in an unremarkable overall difference of %UF between groups. (2) Physicians are less likely to prescribe sequential UF model, which may decrease the risk of IDH, for patients with higher initial BP comparing to those with lower BP. (3) Patients with higher initial BP are more likely to tolerate a SBP decrease >20 mmHg during HD. Probably they are less likely to feel discomfort secondary to intradialytic BP reduction and less frequently to receive management to increase BP.

Strategies for preventing intradialytic hypotension

The major principles to prevent IDH include setting appropriate dry weight, minimizing interdialytic weight gain, avoiding antihypertensive agents before HD, treating underlying heart diseases, and pharmacological intervention with midodrine (an alpha-adrenergic agonist). Besides, optimization of HD therapy, pharmacological intervention, and renal sympathetic denervation might also be considered regarding the role of chronic sympathetic nervous overactivity on IDH [18].

Limitations

The current study has some limitations. First, HRV indices may be affected by dysrhythmia and some antihypertensive agents such as beta-blockers, angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers. We had excluded patients with dysrhythmia at enrollment, but we did not exclude patients taking these anti-hypertensive agents due to the restriction of case numbers. However, the percentage of these drugs usage is similar in the three groups (Table 1). Second, the HRV indices were only measured in one session of HD. HRV gathered from more sessions of HD might increase the stability and reliability of the data. Third, the BPs were checked every 30 min, and HRV measurement were performed for only three times at initial, middle, and late phases in the index HD. Thus, we could not provide the information regarding the HRV changes exactly at the moment of intradialytic BP change. Fourth, the sympathetic tone in participants was not evaluated by certain direct methods such as recording muscle sympathetic nerve activity or checking plasma norepinephrine levels, which may be able to confirm the association between sympathetic nervous activity and intradialytic BP change. However, these direct methods are invasive and less practically available, and their predictive values have yet to be determined [18]. Fifth, although we have taken some important factors for IDH (such as diabetes mellitus, heart failure, serum and dialysate electrolyte concentrations) for adjustment in multivariate regression model, some factors other than sympathetic activity and arterial baroreflexes, such as non-baroreflex or non-autonomic pathways, still existed and disturbed the representation of sympathetic nervous system via HRV [35]. Sixth, higher BP is associated with lower HRV values in most indices in current study. Although variance and LF/HF ratio spoke for themselves in the multivariate analysis regarding their associations with IDH, which were independent from the effect of high BP, the associations among baseline BP, HRV values, and IDH are worth further evaluating.

Conclusions

Autonomic nervous dysfunction is associated with intradialytic BP change. HRV may be a simple and useful indicator for IDH among chronic HD patients.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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