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Impaired heart rate variability in patients with non-diabetic chronic kidney disease — Prominent disruption of vagal control and daily fluctuation

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ABSTRACT

Background: The circadian autonomic fluctuation in chronic kidney disease (CKD) patients has not yet been fully elucidated. The aim of this study was to compare the autonomic fluctuation using heart rate variability between patients with and without CKD.
Methods: The study population consisted of consecutive 101 non-diabetic CKD patients (Stages 3–5, 54 males, 70 ± 10 years) and 129 age- and sex-matched controls without CKD (65 males, 68 ± 10 years) who underwent 24-hour Holter monitoring. The proportion of successive normal sinus NN intervals that differ >50 ms (pNN50) and the high-frequency component (HF) were adopted as vagal parameters. The low- to high-frequency ratio (LF/HF ratio) was evaluated as a sympatho-vagal balance parameter. To evaluate the direct contribution of CKD and other comorbidities to the autonomic variation, the regression analysis was performed after we arbitrarily divided 24 h into night-time (10 PM–8 AM) and day-time (8 AM–10 PM).
Results: The CKD patients had higher prevalence of hypertension, hyperuricemia, and low hemoglobin as compared to controls ($P < 0.05$). Both groups showed surges of pNN50 and HF nocturnally. However, these nocturnal surges were significantly suppressed in CKD ($P < 0.05$), reflecting the impaired vagal activity. Regression analysis demonstrated an independent relation between the nocturnal reduction of vagal parameters and CKD ($P < 0.05$), and also revealed that the LF/HF ratio was not related to CKD ($P > 0.05$), but to low Hb ($P < 0.05$).
Conclusion: The circadian autonomic, particularly vagal, fluctuations were impaired in non-diabetic CKD patients independently from aging and comorbidities. Further research is required to assess the association between this impairment and prognosis of CKD patients.

1. Introduction

Chronic kidney disease (CKD) has been associated with disturbed autonomic control that is linked to an increased risk of sudden cardiac death (SCD) [1,2,3]. Moreover, the incidence of cardiac events or death is reported more frequently in the morning in patients with CKD [4]. This circadian variation of cardiac events and death may be related to the autonomic circadian variation. In addition, dialysis patients have been reported to have a higher prevalence of abnormal heart rate variability (HRV) [5].

In the last two decades, autonomic evaluation through HRV, considered to reflect autonomic activation, has been conducted in patients undergoing hemodialysis, demonstrating that a decreased HRV was associated with higher mortality, even after adjusting for the presence of diabetes mellitus (DM) [6]. Renal failure and hemodialysis patients showed decreased HRV [7], independent of diabetic neuropathy. Moreover, regular hemodialysis itself can directly affect HRV [8], therefore circadian HRV in CKD patients not undergoing hemodialysis may differ from that of CKD patients on hemodialysis. However, the exact relationship between non-diabetic CKD, end-stage renal failure, and HRV remains to be clarified, even though autonomic disturbances in patients on hemodialysis have already been reported.

In this study, we aimed at 1) evaluating the circadian variation of cardiac autonomic function in non-diabetic CKD patients by analysis of 24-hour Holter electrocardiograms (ECG); 2) comparing the cardiac

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Table 1
Baseline patient characteristics.

	CKD (+) N = 101	CKD (−) N = 129	P value
Male	54 (53%)	65 (50%)	0.64
Age (years)	70.1 ± 10.0	68.1 ± 10.4	0.14
Estimated GFR (mL/min/1.73 m^2)	39.2 ± 16.0	75.6 ± 9.7	<0.001
On hemodialysis	5 (5%)	0 (0%)	0.011
Height (cm)	160.2 ± 9.1	160.2 ± 9.5	0.98
Body weight (kg)	56.5 ± 12.5	57.4 ± 13.2	0.65
Body mass index	21.9 ± 3.6	22.2 ± 3.7	0.51
Mean heart rate (bpm)	70.6 ± 10.3	71.6 ± 9.7	0.40
Hypertension	61 (60%)	54 (42%)	0.0053
Systolic blood pressure (mm Hg)	126 ± 19	128 ± 17	0.58
Diastolic blood pressure (mm Hg)	70 ± 12	75 ± 11	0.002
Hyperuricemia	32 (32%)	3 (2%)	<0.001
Dyslipidemia	40 (40%)	42 (33%)	0.27
Ischemic heart disease	10 (10%)	12 (9%)	0.88
Hb (g/dL)	12.3 ± 2.2	13.6 ± 1.5	<0.001

autonomic function between individuals with and without CKD; and 3) evaluating the direct relationship between the presence of CKD and autonomic disturbance using multivariate regression analysis.

2. Methods

2.1. Study population

The study population consisted of patients who underwent 24-hour Holter ECGs between 2009 and 2011, with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [9].

These patients were compared against an age- and sex-matched control group who were randomly selected from patients who underwent 24-hour Holter ECGs between January 2010 and June 2010, and who had eGFR ≥60 mL/min/1.73 m^2.

Patients with over 2000 presystolic atrial or ventricular complex (PAC or PVC, respectively) beats per day, or with over 3000 PAC and PVC per day in total were excluded. Other exclusion criteria included type 1 or 2 DM, congenital heart disease, atrial fibrillation, significant heart valve disease, hospital admission due to congestive heart failure within 6 months, and β-blocker use.

2.2. Clinical data

Baseline clinical information was collected retrospectively based on clinical records. Ambulant blood pressure and hemoglobin (Hb) was recorded. eGFR was determined based on the new Japanese coefficient-modified Modification of Diet in Renal Disease (MDRD) study equation [10]. The presence of ischemic heart disease was defined as a history of over 75% stenosis in a coronary artery diagnosed on coronary angiography or coronary CT.

2.3. Echocardiography

In all patients and controls, cardiac chamber quantification by 2D echocardiography was performed according to guidelines provided by the American Society of Echocardiography [11]. Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVEDS), diastolic posterior left ventricular wall thickness (PWT), diastolic interventricular septum thickness (SWT), LV ejection fraction (LVEF), and LV mass were assessed. The LV mass was calculated as follows: LV mass (g) = $0.8 \times [1.04 \times \{(\mathrm{LVEDD} + \mathrm{PWT} + \mathrm{SWT})^3 - (\mathrm{LVEDD})^3\}] + 0.6$.

2.4. Holter ECG analysis

Holter ECG was retrospectively analyzed by a medical technologist blinded to patient information, and results were confirmed by a cardiologist. The analysis was performed using the SCM-8000 system (Fukuda Denshi, Tokyo, Japan).

The following indices were analyzed every hour over a 24 h period.

Time domain analysis: heart rate (HR), standard deviation of the NN interval (SDNN), proportion of NN50 (the number of pairs of successive NNs that differ by >50 ms divided by the total number of NNs; pNN50).

Frequency domain analysis: low-frequency component (LF; 0.03–0.15 Hz), high-frequency component (HF; 0.15–0.4 Hz), LF/HF ratio.

To evaluate the circadian fluctuation of cardiac autonomic function, the 24 h period was arbitrary divided into day-time (8–22 o'clock) and night-time (22–8 o'clock).

2.5. Statistical analysis

The chi-square test, Student *t* test, or 1-way analysis of variance was performed when appropriate. If the response variables were not normally distributed, a logarithmic transformation of the outcome variable was used to obtain normal distribution. Continuous data were shown as mean ± SD for normally distributed data, and as median values [first quartile–third quartile] otherwise. A significance level of 5% was used for global test statistics.

All authors had full access to the data, and have read and agreed to the manuscript as written. The study was approved by the Tokyo University Hospital Institutional Review Board.

3. Results

3.1. Patient characteristics

101 CKD patients and 129 controls were enrolled in this study. Baseline patient characteristics are shown in Table 1. The number of patients with Stages 3, 4, and 5 CKD were 76, 10, and 15, respectively

Although the prevalence of hypertension was significantly higher in CKD patients, the ambulant diastolic blood pressure was significantly lower (P = 0.0020). CKD patients had lower Hb (P < 0.001).

There were no significant differences in LV dimensions, LVEF, and left atrial diameter (Table 2), however the LV wall was significantly thicker and LV mass was larger in CKD patients.

3.2. Time domain analysis

Although there were no significant differences in the average HR over a 24-hour period between the two groups (70.6 ± 10.3 bpm in CKD patients vs 71.6 ± 9.7 bpm in controls, P = 0.40), the HR in CKD patients was significantly lower compared to controls during the day-time periods on hourly analysis (Fig. 1a).

The SDNN over a 24-hour period of CKD patients was significantly lower compared to controls (115.3 ± 39.1 ms vs 131.5 ± 31.8 ms, P < 0.001). On hourly analysis, SDNN of CKD patients was significantly

Table 2
Echocardiographic characteristics.

	CKD (+) N = 101	CKD (−) N = 129	P value
LVEDD (mm)	45.9 ± 6.0	44.6 ± 4.7	0.10
LVEDS (mm)	28.0 ± 5.7	26.7 ± 4.2	0.077
SWT (mm)	10.3 ± 2.0	9.2 ± 1.8	<0.001
PWT (mm)	9.8 ± 1.8	9.1 ± 1.3	0.006
Left ventricular mass (g)	161 ± 47	138 ± 43	<0.001
Ejection fraction (%)	68.8 ± 10.0	70.3 ± 8.3	0.27
Left atrial diameter (mm)	38.3 ± 7.4	36.3 ± 6.2	0.051

lower at the beginning of or just before sleep (22–23 o'clock) and in the early morning (5–9 o'clock) (Fig. 1b).

The pNN50 over a 24-hour period of CKD patients trended lower compared to controls (2.1 [0.5–4.9] vs 2.8 [0.9–6.1], P = 0.064), and was significantly lower compared to controls throughout the night-time period (22–6 o'clock) on hourly analysis (Fig. 1c).

These results suggest that vagal activation during night-time and the early morning period in CKD patients was lower compared to controls.

3.3. Frequency domain analysis

HF and LF over a 24-hour period of CKD patients were significantly lower compared to controls (112.5 [54.1–166.0] vs 159.0 [95.5–268.9], P < 0.001, 174.4 [85.6–260.6] vs 233.2 [155.6–441.6], P < 0.001, respectively).

HF demonstrated significant differences between the evening and early morning periods on hourly analysis (Fig. 2a). The difference between the two groups became larger particularly during midnight.

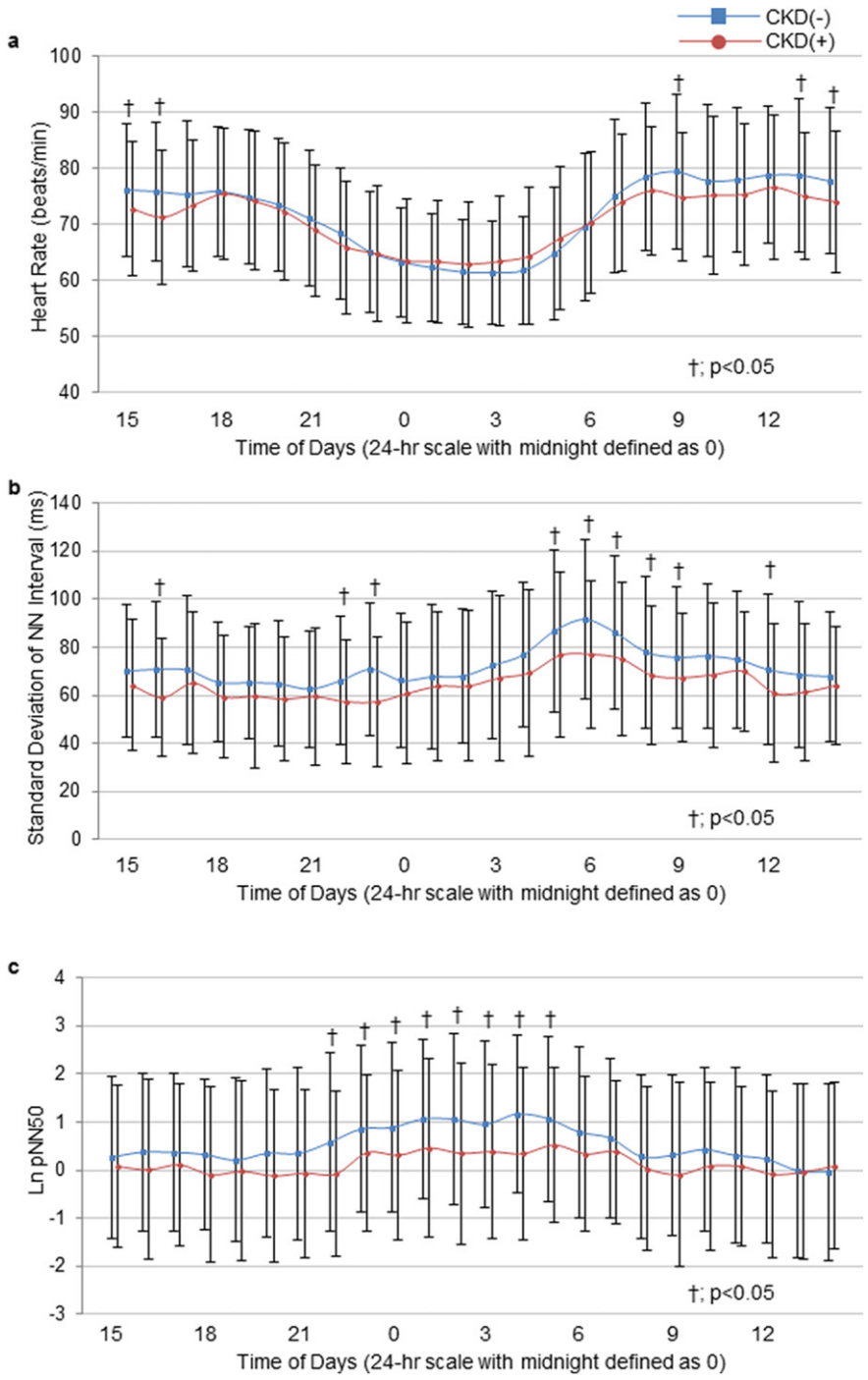

Fig. 1. Time trends of time domain parameters over 24 h. a: The heart rate in patients with CKD was significantly lower during day-time. The heart rate during night-time showed no significant differences. b: The SDNN in patients with CKD was significantly lower at the beginning of sleep and in the early morning. The deviation between the two groups was the largest in the early morning. c: The pNN50 in patients with CKD was significantly diminished during night-time. †: P < 0.05 between patients with CKD and without CKD. CKD = chronic kidney disease.

LF in CKD patients was significantly smaller compared to controls throughout a 24-hour period (Fig. 2b).

The LF/HF ratio over a 24-hour period of CKD patients trended lower compared to controls (1.6 [0.8–2.4] vs 1.8 [1.1–2.7], P = 0.076).

On hourly analysis, the LF/HF ratio in CKD patients was significantly lower compared to controls during day-time (Fig. 2c). Interestingly, the LF/HF ratio showed no significant differences during night-time except at 2 o'clock.

This data suggests that vagal activation in CKD patients was lower compared to controls, and the sympatho-vagal balance difference between day-time and night-time periods in CKD patients was smaller compared to controls.

3.4. Circadian fluctuation

pNN50 during day-time was significantly associated with the presence of hypertension after adjusting for age (Table 3). CKD was not a significant index of pNN50 during day-time. However, pNN50 during night-time was significantly and independently associated with male sex and CKD.

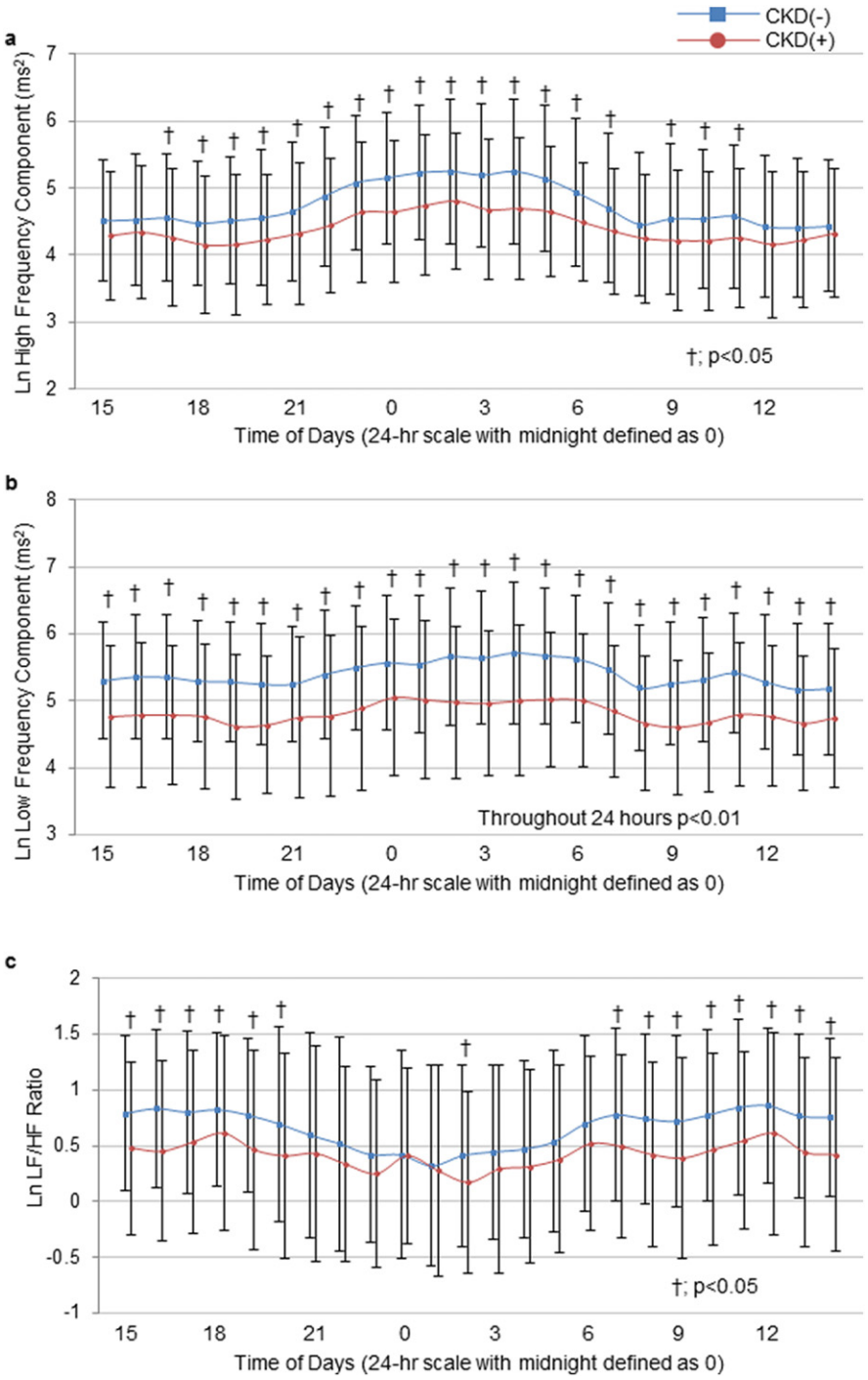

Fig. 2. Time trends of frequency domain parameters over 24 h. a: The HF in patients with CKD was significantly diminished almost throughout most of the 24 h. The deviation between the 2 groups was the largest during night-time. b: The LF in patients with CKD was significantly diminished over 24 h. c: The LF/HF ratio in patients with CKD was significantly lower during day-time. †: P < 0.05 between patients with CKD and without CKD. CKD = chronic kidney disease.

CKD was associated with reduced HF during day-time and was significantly associated with reduced HF during night-time after adjusting for age and Hb (Table 4).

The LF/HF ratio did not show a significant relationship with CKD after adjusting for age, Hb, and sex (Table 5). Anemia and older age were significantly associated with a lower LF/HF ratio.

These results from regression analysis suggest that CKD independently affected vagal activation, particularly during night-time, however, did not affect the sympatho-vagal balance.

4. Discussion

The major findings of our study are the following: 1.) HRV parameters of non-diabetic CKD patients, which were related to cardiac vagal function, were significantly lower during night-time compared to those without CKD; 2.) non-diabetic CKD was an independent factor for reduction of cardiac vagal function, particularly during night-time; and 3.) sympatho-vagal balance was not affected by CKD, but by anemia.

To the best of our knowledge, this is the first detailed report investigating the direct relationship between circadian cardiac vagal activity and non-diabetic renal dysfunction, and the abnormal circadian fluctuation of cardiac vagal activation in non-diabetic CKD patients.

4.1. Cardiac autonomic disturbance in CKD patients

Sympathetic overactivity in CKD patients has been previously demonstrated by measuring sympathetic-nerve discharge [3] and by an increase in catecholamine concentration [12].

The LF/HF ratio has been utilized to evaluate cardiac sympatho-vagal balance through HRV, although it remains debatable if it could be used as a marker of cardiac sympathetic activity [13]. In our study, CKD patients showed a significantly lower HR and LF/HF ratio during day-time (Figs. 1a, 2c). A higher HR in individuals without CKD may be secondary to a more active day-time period, leading to a higher LF/HF ratio reflecting higher sympathetic activity. In fact, the LF/HF ratio was not significantly associated with CKD after adjusting for HR.

There were no significant differences in night-time HR between the 2 groups. Although the prevalence of hypertension was higher in CKD patients, the blood pressure itself was well controlled with medical therapy, and left ventricular function was well preserved. This could explain the night-time HR data. We have to emphasize that there were significant discrepancies in vagal parameters during night-time despite similar HR between the two groups.

In our study, not only were the vagal parameters in CKD patients significantly lower, but LF was also significantly diminished throughout 24 h. Although Vita et al. also showed that LF in hemodialysis patients was significantly reduced, no significant differences in HF and the LF/HF ratio were demonstrated [14]. This discrepancy could be attributed to differences in the patient population.

The presence of hypertension, obesity or diabetes mellitus, aging, and the LV mass has been reported to affect the HRV [15]. The regression analysis incorporating these indices showed that the vagal disturbance was independently associated with the presence of CKD.

These comorbidities and factors showed no significant association with HRV in our study. This can be attributed to optimal control with medical therapy of the included patients, as shown in Tables 1 and 2.

The mechanism of vagal disturbance in patients with CKD has not yet been clarified. The data in the present study may reflect a higher sympathetic activity, which subsequently suppressed the vagal activity as the result of interaction.

4.2. Circadian fluctuation of HRV in CKD patients

Circadian disturbance of HRV has been reported in patients with DM, obstructive sleep apnea, and ischemic heart disease [16,17]. In our study, vagal surge during night-time was diminished in CKD patients and corresponded to the report from Roumelioti et al. [18], which included more severe CKD and diabetic patients.

Abnormal circadian fluctuation in CKD patients could affect the occurrence of SCD [4]. Lack of vagal surge during night-time and in the early morning may explain a higher SCD occurrence during these times.

CKD patients had thicker LV walls, which might reflect pressure overload. A previous report demonstrated that cardiac filling pressure affected sympathetic activity through norepinephrine spillover [19]. CKD patients could have higher filling pressures, resulting in lower vagal activation.

The LF/HF ratio, which was considered to partially reflect sympatho-vagal balance, was not associated with CKD (Table 5). We incorporated Hb as a parameter and showed that lower Hb conditions resulted in lower LF/HF, which corresponds to previous reports of anemia-associated reduction of HRV [20].

Normally, lower LF/HF reflects lower sympathetic activity or higher vagal activity. However, as previously reported, remarkable HRV reduction, including LF/HF, was demonstrated in CKD patients. Moreover, lower LF/HF was reported to be associated with poorer prognosis [1,21]. Our data suggests that this LF/HF reduction was associated not with CKD but with anemia. In fact, Furuland et al. demonstrated that Hb normalization improved HRV in CKD patients [22].

In addition, apparent day-time LF/HF reduction in our study was considered to be due to significantly low LF. LF is known to be affected not only by sympathetic activation, but also by parasympathetic activation [23]. The detailed mechanism of LF/HF modulation in CKD patients should be further investigated.

4.3. Clinical implications

A recent study demonstrated that primary prevention of SCD utilizing implantable cardioverter-defibrillators can improve the prognosis of

Table 3
Association between clinical characteristics and pNN50.

	Day-time		Night-time	
	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value
Hypertension	**0.69 [0.53–0.88]**	**0.0036**	0.81 [0.64–1.03]	0.083
Male	0.77 [0.58–1.03]	0.08	**0.73 [0.56–0.97]**	**0.027**
Age (10 years)	1.24 [0.97–1.58]	0.084	1.06 [0.84–1.33]	0.62
Hyperuricemia	1.29 [0.90–1.86]	0.17	1.35 [0.96–1.91]	0.088
Chronic kidney disease	0.88 [0.67–1.16]	0.37	**0.73 [0.56–0.95]**	**0.02**
Left ventricular mass (10 g)	1.02 [0.96–1.09]	0.45	1.01 [0.95–1.06]	0.85
Ischemic heart disease	0.87 [0.58–1.29]	0.48	0.83 [0.57–1.21]	0.33
Dyslipidemia	1.08 [0.82–1.41]	0.59	1.09 [0.84–1.41]	0.5
Hemoglobin (1 g/dL)	1.00 [0.86–1.16]	0.99	1.12 [0.97–1.28]	0.12

Bold values indicate level of significance = 5%

Table 4
Association between clinical characteristics and HF.

	Day-time		Night-time	
	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value
Hypertension	**0.85 [0.74–0.98]**	**0.024**	0.93 [0.80–1.07]	0.32
Chronic kidney disease	**0.86 [0.74–1.00]**	**0.057**	**0.81 [0.69–0.95]**	**0.0086**
Male	0.89 [0.76–1.05]	0.16	0.88 [0.74–1.03]	0.12
Age (10 years)	1.06 [0.93–1.21]	0.37	0.95 [0.83–1.09]	0.48
Left ventricular mass (10 g)	1.01 [0.98–1.05]	0.38	0.99 [0.96–1.02]	0.58
Hyperuricemia	1.07 [0.88–1.30]	0.51	1.11 [0.90–1.37]	0.31
Dyslipidemia	0.95 [0.82–1.10]	0.52	0.97 [0.83–1.13]	0.66
Hemoglobin (1 g/dL)	0.99 [0.91–1.07]	0.77	1.04 [0.96–1.13]	0.37
Ischemic heart disease	0.99 [0.80–1.23]	0.92	0.99 [0.79–1.25]	0.96

Bold values indicate level of significance = 5%

Table 5
Association between clinical characteristics and LF/HF ratio.

	Day-time		Night-time	
	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value
Age (10 years)	**0.83 [0.75–0.91]**	**<0.001**	**0.90 [0.81–0.99]**	**0.024**
Hemoglobin (1 g/dL)	**1.08 [1.02–1.15]**	**0.0053**	**1.07 [1.01–1.14]**	**0.016**
Male	**1.11 [1.00–1.24]**	**0.057**	**1.19 [1.06–1.33]**	**0.0028**
Chronic kidney disease	0.93 [0.84–1.04]	0.19	0.98 [0.87–1.09]	0.65
Left ventricular mass (10 g)	0.99 [0.97–1.01]	0.37	1.00 [0.98–1.03]	0.79
Hyperuricemia	0.97 [0.84–1.11]	0.62	0.94 [0.82–1.09]	0.42
Dyslipidemia	0.99 [0.89–1.09]	0.78	0.96 [0.86–1.06]	0.39
Ischemic heart disease	0.99 [0.85–1.15]	0.86	0.91 [0.78–1.07]	0.26
Hypertension	0.99 [0.90–1.09]	0.91	0.98 [0.89–1.08]	0.69

Bold values indicate level of significance = 5%

heart failure patients without CKD, however not in CKD patients [24]. Therefore, a different approach is required.

Our study demonstrated impairment of cardiac autonomic, particularly vagal, function in CKD patients. Further evaluation of the outcome of CKD patients and its relationship with the autonomic circadian impairment should be conducted.

This verification may lead to the introduction of autonomic modulation therapy to decrease not only the incidence of SCD, but also the deteriorative consequence in renal outcomes in CKD patients [21].

Indeed, Gronda et al. have recently reported that baroreflex activation therapy improved clinical parameters in heart failure patients [25]. Patients with heart failure have impaired autonomic function, and this has been shown to be associated with poor prognosis. Thus, the impaired cardiac autonomic activity in CKD patients, which we have demonstrated in our study, could be a possible therapy target in the future.

4.4. Limitations

The present study has several limitations. This was a single-center study and a small patient cohort. The association of autonomic dysfunction and prognosis could not be analyzed, as patient follow-up was not the end-point of our study. As previously mentioned, it is complicated to discuss the nature of the cardiac autonomic system with power spectral analysis [13]. Future research with multi-center and larger patient numbers should be performed to confirm that autonomic dysfunction in patients with non-diabetic CKD affects prognosis. Due to the retrospective analysis, no data on obstructive sleep apnea was available, which can affect the autonomic nervous system [26]. However, we have consecutively included CKD patients, therefore we believe that the data should be reflective of real-world CKD patients.

Statement of competing financial interests

The authors have no conflict of interests regarding this study.

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