Effect of Sympatholytic Therapy on Circadian Cardiac Autonomic Activity in Non-Diabetic Chronic Kidney Disease

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Summary

Although beta-blockade itself is not a first choice for chronic kidney disease (CKD) patients, alpha-beta-blockers (ABB) do improve their prognoses. This study's aim was to evaluate the effect of beta-selective-blockers (BSB) and ABB on circadian cardiac autonomic activity in CKD patients.

The study consisted of 496 non-diabetic individuals who underwent 24-hour Holter monitoring (149 CKD patients and 347 controls without CKD). Using heart rate variability analysis, we evaluated the proportion of NN50 and the high-frequency component (reflecting parasympathetic activity), and low- to high-frequency ratio (reflecting sympathovagal balance). These indices were evaluated by regression analysis incorporating gender, age, related comorbidities, and medications. BSB increased vagal activity only in the day-time and not the night-time in controls. In CKD patients, BSB was significantly related to higher vagal activity throughout the day and with lower sympathovagal balance at night. The night sympathovagal balance of CKD patients taking ABB was significantly higher than that of CKD patients taking BSB, which was the only significant difference between the effects of BSB and ABB.

The sympatholytic therapy effect is different depending on CKD presence and whether patients are treated with BSB or ABB. In CKD patients without severe heart failure, BSB could be associated with higher parasympathetic activity and lower sympathovagal balance compared to ABB.

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Key words: Cardiac autonomic function, Kidney dysfunction, Heart rate variability, β -blocker

Heart failure patients with higher sympathetic activity experience higher mortality.^{1,2)} Treatment with β -blockers improves these patients' outcomes.³⁾ The current guidelines recommend the use of β -blockade as a class IA indication.⁴⁾

Patients with higher sympathetic activity and chronic kidney disease (CKD) also experience higher mortality.⁵⁾ However, in contrast to heart failure patients, β -blockers are not recommended as first line therapy for CKD patients.⁶⁾ Instead, clinicians favor renin-angiotensin system blockers; in fact, previous studies demonstrated that Atenolol is not as effective at slowing renal disease progression compared to Lisinopril and calcium channel blockers.⁷⁾

Recently we reported higher cardiac sympathetic activity and impaired parasympathetic activity in CKD patients.⁸⁾ Based on these results, lowering sympathetic ac-

tivity in CKD patients may result in a prognostic improvement. Wali, *et al.* reported that $\alpha\beta$ -blockers (ABB) improved outcomes in heart failure patients with CKD.⁹⁾

β -blockers decrease all-cause and cardiovascular mortality in CKD patients who have heart failure with reduced left ventricular ejection fraction (LVEF).¹⁰⁾ However, it has not yet been clarified whether the use of β -blockers would benefit CKD patients without heart failure.

In this study, we compared the sympatholytic effect of β -blocking agents in CKD patients without heart failure to non-CKD individuals using heart rate variability (HRV) analysis. We also evaluated the difference between the effects of β -selective β -blockers (BSB) and ABB on cardiac autonomic function.

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Table I. Patients Characteristics

	Group-NKD <i>n</i> = 347	Group-KD <i>n</i> = 149	<i>P</i> value
Male	150 (43%)	80 (54%)	0.032
Age (years)	58.6 ± 15.4	70.6 ± 10.8	< 0.0001
Hypertension	133 (38%)	97 (65%)	< 0.0001
sBP (mmHg)	126 ± 18	127 ± 18	0.73
dBP (mmHg)	75 ± 12	70 ± 11	< 0.0001
Dyslipidemia	99 (29%)	59 (40%)	0.016
Hyperuremia	16 (5%)	44 (30%)	< 0.0001
Ischemic heart disease	23 (7%)	24 (16%)	0.0010
LVEF (%)	70 ± 8	69 ± 10	0.55
LV Mass (g)	143.0 ± 45.1	164.6 ± 53.6	< 0.0001
Hemoglobin (g/dL)	13.4 ± 1.6	12.5 ± 1.9	< 0.0001
Serum creatinine (mg/dL)	0.69 ± 0.15	1.72 ± 1.85	< 0.0001
eGFR	80.5 ± 17.8	41.2 ± 15.4	< 0.0001
ACEi/ARB	83 (24%)	80 (54%)	< 0.0001
β-selective-blocking agent	24 (7%)	26 (17%)	0.0004
αβ-blocking agent	19 (5%)	15 (10%)	0.064
Ca antagonist	70 (20%)	77 (52%)	< 0.0001

Chronic kidney disease patients were older and had significantly more comorbidities and drug therapies (see text for details).

Methods

Study population: The study population consisted of consecutive patients who underwent 24-hour holter ECGs between 2009 and 2011. The study was approved by the local Institutional Review Board. Patients meeting the following criteria were excluded from the study:

- Over 2,000 presystolic atrial or ventricular complex (PAC or PVC, respectively) beats per day
- Over 3,000 PAC and PVC per day
- Type 1 or 2 diabetes mellitus
- Congenital heart disease
- Atrial fibrillation
- Significant heart valve disease
- Hospital admission due to acute renal failure or congestive heart failure within the previous three months
- Chronic heart failure with New York Heart Association Functional Classification (NYHA) grade III or IV symptoms.

We enrolled 496 consecutive patients in this cohort study, assigning 149 patients with < 60 mL/minute/1.73 m² to Group-KD and 347 individuals with ≥ 60 mL/minute/1.73 m² to Group-NKD. The number of patients with stage 3, 4, and 5 CKD were 120, 13, and 16 respectively. Patients' characteristics are shown in Table I.

Clinical data: Baseline clinical information was collected retrospectively based on clinical records. Ambulant blood pressure and hemoglobin (Hb) were recorded. eGFR was determined based on the new Japanese coefficient-modified Modification of Diet in Renal Disease (MDRD) study equation.¹¹⁾ Ischemic heart disease was defined as a history of over 75% stenosis in a coronary artery diagnosed on coronary angiography or coronary CT.

Echocardiography: We collected cardiac chamber quantification data using 2D echocardiography, which was performed according to American Society of Echocardiography guidelines.¹²⁾ Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension

(LVESD), diastolic posterior left ventricular wall thickness (PWT), diastolic interventricular septum thickness (SWT), LVEF, and LV mass were assessed. The LV mass was calculated as follows:

$$\text{LV mass (g)} = 0.8 \times [1.04 \times \{(\text{LVEDD} + \text{PWT} + \text{SWT})^3 - (\text{LVEDD})^3\}] + 0.6.$$

Holter ECG analysis: Holter ECG was retrospectively analyzed by a medical technologist blinded to patient information, and the results were confirmed by a cardiologist. The analysis was performed using the SCM-8000 system (Fukuda Denshi, Tokyo, Japan). The following indices were analyzed hourly over a 24-hour 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 > 50ms 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 hour period was arbitrarily divided into day-time (8-22 o'clock) and night-time (22-8 o'clock).

Statistical analysis: The chi-square test, Student *t* test, or 1-way analysis of variance was performed when appropriate. For post-hoc analysis, we adopted the Tukey-Kramer test to evaluate statistical differences among three groups depending on the medications. If the response variables were not normally distributed, we used a logarithmic transformation of the outcome variable 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.

Due to this cohort study's characteristics and heterogeneous patient population, we performed logistic regression analysis to identify independent factors contributing to the HRV parameters. Sexuality, age, comorbidities, he-

Table II. Patient Characteristics according to Medications

	Group-NKD				Group-KD			
	No SLM <i>n</i> = 304	BSB <i>n</i> = 24	ABB <i>n</i> = 19	<i>P</i> value	No SLM <i>n</i> = 108	BSB <i>n</i> = 26	ABB <i>n</i> = 15	<i>P</i> value
Male	122 (40%)	14 (58%)	14 (74%)	0.0050	59 (55%)	10 (39%)	11 (73%)	0.091
Age (years)	57.9 ± 15.5	64.1 ± 15.3	62.9 ± 12.3	0.076	70.1 ± 10.4	71.5 ± 12.3	73.1 ± 10.8	0.53
Hypertension	106 (35%)	16 (67%)	11 (58%)	0.0017	64 (59%)	22 (85%)	11 (73%)	0.040
sBP (mmHg)	126 ± 18	124 ± 18	128 ± 7.8	0.77	126.0 ± 18.6	130.4 ± 15.2	124.7 ± 21.1	0.51
dBP (mmHg)	75 ± 12	70 ± 11	77 ± 8.6	0.088	69.7 ± 12.0	71.5 ± 8.2	66.9 ± 9.8	0.47
Dyslipidemia	82 (27%)	8 (33%)	9 (47%)	0.14	43 (40%)	9 (35%)	7 (47%)	0.75
Hyperuremia	12 (4%)	1 (4%)	3 (16%)	0.058	33 (31%)	6 (23%)	5 (33%)	0.71
Ischemic heart disease	17 (6%)	3 (13%)	3 (16%)	0.11	10 (9%)	8 (31%)	6 (40%)	0.0008
LVEF (%)	70 ± 8	70 ± 8	65 ± 14	0.044	70 ± 9	69 ± 12	65 ± 13	0.25
LV Mass (g)	141.0 ± 44.3	138.0 ± 41.1	177.9 ± 49.1	0.0040	158.8 ± 46.4	168.0 ± 56.5	194.4 ± 79.2	0.065
Hemoglobin (g/dL)	13.4 ± 1.7	13.4 ± 1.1	13.5 ± 1.6	0.98	12.5 ± 2.1	12.4 ± 1.7	12.8 ± 1.5	0.79
Serum creatinine (mg/dL)	0.68 ± 0.15	0.74 ± 0.12	0.75 ± 0.14	0.047	1.81 ± 2.00	1.59 ± 1.76	1.32 ± 0.46	0.58
eGFR	81.1 ± 18.4	74.9 ± 12.4	77.8 ± 12.9	0.20	40.3 ± 15.8	43.7 ± 15.9	42.7 ± 11.8	0.57
ACEi/ARB	61 (20%)	9 (38%)	13 (68%)	< 0.001	52 (48%)	18 (69%)	10 (67%)	0.088
β-selective-blocking agent	0 (0%)	24 (100%)	0 (0%)		0 (0%)	26 (100%)	0 (0%)	
αβ-blocking agent	0 (0%)	0 (0%)	19 (100%)		0 (0%)	0 (0%)	15 (100%)	
Ca antagonist	57 (19%)	7 (29%)	6 (32%)	0.21	50 (46%)	18 (69%)	9 (60%)	0.087

In Group-NKD and Group-KD, patients' characteristics were compared between patients without sympatholytic medications (SLM), with beta-selective-blockers (BSB), and with alpha-beta-blockers (ABB). *P*-value is based on the analysis of variance. See text for details.

moglobin value, echocardiographic parameters, and medications (ABB, BSB, renin-angiotensin system inhibitors) were incorporated in the single variable regression analysis. For the multivariable regression analysis, we included the variables indicating statistical significance in the single variable regression analysis. Data analyses were performed using JMP® (SAS, Version 10, USA).

All authors had full access to the data, and have read and agreed to the manuscript as written.

Results

Patient population: Group-KD included older men with higher prevalence of hypertension, dyslipidemia, hyperuricemia, and diagnosed ischemic heart disease compared to Group-NKD. Although there was no significant difference in the mean LVEF, LV mass was significantly higher in Group-KD. Only 6 patients had reduced LVEF < 40% (4 in Group-KD, 2 in Group-NKD). Serum hemoglobin was significantly lower in Group-KD, and these patients took more medications as shown in Table I.

Table II shows the results of the subgroup comparison of patients' characteristics. In both Group-KD and Group-NKD, the patients who took β-blocking agents more frequently had hypertension. In Group-NKD, the patients under β-blocker therapy had larger LV-mass and were simultaneously taking renin-angiotensin inhibitors, and in Group-KD, tendency regarding these parameters were noted.

β-blockers: Fifty patients took BSB (Table II). Out of these 50 patients, bisoprolol, atenolol, metoprolol, and celiprolol were taken by 28, 17, 3, and 2 patients, respectively. The daily dose of bisoprolol, atenolol, metoprolol, and celiprolol were 2.5-5 mg, 12.5-50 mg, 20-40 mg, and 200 mg, respectively. The only patients who did not take BSB drugs in the morning were those on atenolol 50 mg (*n* = 1) and celiprolol with 200 mg (*n* = 2); they took

their drugs twice daily (morning and evening). Thirty-four patients took 5-10 mg of carvedilol as an ABB every morning (Table II).

Heart rate parameters: The HR according to β-blocking agents are shown in Figure A. In both Group-KD and Group-NKD, the patients taking β-blocking agents had lower HR.

The frequency domain analysis results are shown in Figure B. In Group-KD, HF increased with the administration of β-blocking agents, particularly in patients taking BSBs, not only during the day-time but also during the night-time. In comparison, HF was increased by BSB only during the day-time in Group-NKD.

LFs according to β-blocking agents are shown in Figure C. Notably, β-blocking agents increased LF in Group-KD, although there were no differences in Group-NKD.

The analysis results on LF/HF ratio are shown in Figure D. In Group-KD, the patients taking BSBs had a markedly lower LF/HF ratio during the night-time. In Group-NKD, there was a decrease in LF/HF ratio due to BSB use during the day-time but not during the night-time.

Regression analysis:

HF (Table III) In Group-KD, BSB administration was independently related to higher HF throughout the day, and higher Hb values tended to be related with higher HF. During the night-time, higher Hb values were significantly related to higher HF. ABB did not significantly influence the HF throughout the day.

In Group-NKD, administration of both BSB and ABB significantly and independently increased HF, but only during the day-time. The age and the presence of hyperlipidemia negatively correlated to HF during the day-time. During the night-time, age and male gender were negatively correlated with HF.

There were no significant differences in HF between

Figure. Circadian variation of heart rate (HR) parameters according to sympatholytic medications. **A:** Circadian variation of HR according to sympatholytic medications. Both sympatholytic medications (SLM), beta-selective blockers (BSB), and alpha-beta blockers (ABB) decreased HR during day-time and night-time. There were no significant differences between BSB and ABB. In Group-KD patients, although the baseline HR in the day-time was lower as compared to Group-NKD patients, HR under BSB or ABB treatment was on a comparable level. **B:** Circadian variation of high-frequency component according to SLM. In Group-NKD patients, higher HF during the day-time was noted with BSB treatment. In Group-KD patients, the baseline HF was lower as compared to the patients in Group-NKD and SLM increased HF throughout the day. **C:** Circadian variation of low frequency component according to SLM. In Group-NKD patients, SLM did not affect the LF. In Group-KD patients, LF was higher, but mostly without statistical significance, under SLM treatment. **D:** Circadian variation of low-to-high frequency ratio according to SLM. In Group-NKD patients, BSB decreased the LF/HF ratio particularly during the day-time, but ABB did not obviously alter the LF/HF ratio. In Group-KD patients, BSB lowered the LH ratio during the night-time. ABB did not lower the LF/HF ratio. Moreover, ABB increased the LH ratio as compared to BSB during the night-time. ($\ddagger P < 0.05$, BSB versus no SLM and ABB versus no SLM; $\dagger P < 0.05$, BSB versus no SLM; $* P < 0.05$, ABB versus no SLM; $\star P < 0.05$, BSB versus ABB).

patients who were treated with BSB or ABB.

LF (Table IV) In Group-KD, LF was significantly decreased in the older age group and lower Hb group throughout the day. BSB tended to be related with higher LF only during the day-time.

In Group-NKD, older age, the presence of HL and lower Hb correlated with lower LF throughout the day. The administration of BSB or ABB did not influence LF.

There were no significant differences in HF between patients who were treated with BSB or ABB.

LF/HF Ratio (Table V) In Group-KD, the LF/HF ratio during the day-time was significantly increased in the younger age group and male sex. BSB administration de-

creased the LF/HF ratio only during the night-time. ABB did not affect the LF/HF ratio both during the day-time or night-time.

In Group-NKD, BSB administration was associated with lower LF/HF ratio and the male gender, while higher Hb was associated with higher LF/HF ratio throughout the day. ABB administration was associated with lower LF/HF ratio only during the night-time. The LF/HF ratio during the day-time was lower in the older age group.

Group-KD patients treated with ABB had a significantly higher LF/HF ratio than those who were treated with BSB, which was the only difference between treatment with BSB and ABB.

Table III. Regression Analysis Results (High Frequency)

	Estimates	95% CI	P value
HF in Group-NKD			
Day-time			
Age (1year)	-0.014	-0.021--0.0064	0.0003
β selective blocker	0.34	0.14-0.54	0.0012
$\alpha\beta$ blocker	0.32	0.087-0.55	0.0071
Hyperlipidemia	-0.13	-0.25--0.0019	0.047
LV mass (1g)	-0.0025	-0.0051--0.0000023	0.050
Night-time			
Age	-0.021	-0.028--0.015	< 0.0001
Male	-0.12	-0.22--0.016	0.023
HF in Group-KD			
Day-time			
β selective blocker	0.30	0.093-0.51	0.0049
Hb	0.070	-0.0075-0.15	0.076
Night-time			
β selective blocker	0.40	0.17--0.63	0.0008
Hb	0.10	0.014-0.19	0.023

Logistic regression analyses were performed to test the relevance between clinical factors and heart rate variability. See text for details.

Table IV. Regression Analysis Results (Low Frequency)

	Estimates	95% CI	P value
LF in Group-NKD			
Day-time			
Age (1 year)	-0.024	-0.029--0.018	< 0.0001
Hyperlipidemia	-0.10	-0.20--0.0026	0.044
Hb	0.061	0.0015-0.12	0.045
ACEi/ARB	-0.12	-0.24-0.0076	0.066
Night-time			
Age (1 year)	-0.021	-0.029--0.014	< 0.0001
Hyperlipidemia	-0.15	-0.27--0.024	0.019
Hb	0.075	0.0050-0.15	0.036
LF in Group-KD			
Day-time			
Hb	0.13	0.041-0.21	0.004
Age (1 year)	-0.016	-0.035--0.0014	0.032
β selective blocker	0.19	-0.035-0.41	0.098
Night-time			
Hb	0.14	0.056-0.23	0.0014
Age (1 year)	-0.019	-0.034--0.0048	0.0095
Male	0.15	-0.012-0.32	0.069

Logistic regression analyses were performed to test the relevance between clinical factors and heart rate variability. See text for details.

Discussion

The major findings of this study were: 1) The influences of sympatholytic medication on cardiac autonomic function, as measured by HRV, were different depending on the presence of kidney dysfunction, 2) BSB administration was associated with higher parasympathetic HRV in patients with and without kidney dysfunction, 3) ABB was not associated with higher parasympathetic HRV, 4) BSB was associated with lower sympathovagal balance throughout the day in patients without kidney dysfunction, and only during the night-time in patients with kidney dysfunction, and 5) ABB did not affect sympathovagal balance in patients with kidney dysfunction.

To the best of our knowledge, this is the first detailed

analysis of the effect of sympatholytic medication on patients with kidney dysfunction who do not have heart failure.

In patients with heart failure, sympathetic hyperactivity is related to worse prognosis, and sympathetic denervation improves cardiac function and clinical status.¹³⁾ β -blockers are an established medication for improving patients' outcomes, and their use is not dependent on the presence of CKD.^{4,14)} In contrast, β -blockers are generally not first line treatments for hypertension in CKD patients;¹⁵⁾ rather, medications affecting the renin-angiotensin system are preferable because of their significant renal-protective effects. As a result, β -blockers are recommended for CKD patients as third-line therapy.

Previous studies linked augmented sympathetic activity in CKD patients to poor prognoses.^{5,16)} We have demonstrated that CKD presence can affect baseline circadian autonomic fluctuations.⁸⁾ The vagal function impairment was associated with CKD, and the sympathovagal balance was affected by aging and hemoglobin value. We used these results to investigate the further deviation from these baseline circadian HRV fluctuations due to β -blocker administration.

In CKD patients, the nocturnal drop of sympathovagal balance is attenuated (Figure D). This may result renin-angiotensin system activation and possibly lead to sudden cardiac death in the early morning.¹⁷⁾ Theoretically, inhibiting sympathetic activity could improve CKD patient outcomes, similar to patients with heart failure. The dissociation between the hypothesis and current clinical practice suggests that autonomic function response to β -blockers may be different between CKD and non-CKD patients.

The efficacy of β -blockers, particularly atenolol, is inferior to other classes of antihypertensive drugs in patients with primary hypertension.¹⁸⁾ This inferiority can be attributed to the different characteristic effect on brachial systolic blood pressure and central systolic blood pressure.¹⁹⁾

Table V. Regression Analysis Results (LF/HF Ratio)

	Estimates	95% CI	P value
LF/HF ratio in Group-NKD			
Day-time			
Age (1 year)	-0.0087	-0.014--0.0035	0.0011
Male	0.11	0.023-0.20	0.014
β selective blocker	-0.16	-0.29--0.029	0.017
Hb	0.055	0.0073-0.10	0.024
Night-time			
Male	0.20	0.12-0.28	< 0.0001
Hb	0.052	0.0057-0.098	0.028
$\alpha\beta$ blocker	-0.16	-0.30--0.013	0.033
β selective blocker	-0.14	-0.27--0.0089	0.036
Hypertension	-0.075	-0.15-0.0012	0.054
LF/HF ratio in Group-KD			
Day-time			
Age (1 year)	-0.022	-0.032--0.012	< 0.0001
Male	0.13	0.022-0.24	0.019
Hb	0.047	-0.0082-0.10	0.095
Night-time			
Male	0.21	0.098-0.32	0.0003
Age (1 year)	-0.012	-0.023--0.0024	0.015
β selective blocker	-0.016	-0.30--0.015	0.030

Logistic regression analyses were performed to test the relevance between clinical factors and heart rate variability. See text for details.

However, several studies have demonstrated that the efficacy of vasodilating β -blockers, including carvedilol and nebivolol, is superior to conventional BSB without vasodilating properties.²⁰⁻²² Carvedilol has also been associated with a renal protective effect.^{23,24}

β -blockers and ABB decrease cardiovascular and all-cause mortality in heart failure patients.^{25,26} Renal dysfunction is a frequent comorbidity in patients with severe heart failure, and the concomitant treatment of renin-angiotensin blockers and β -blockers is widespread. In the present study, severe heart failure patients were not included, as shown in Table II; therefore, the patient population differed from those in the aforementioned reports. In terms of CKD patients without left ventricular dysfunction, the advantage of β -blocker administration remains to be clarified. In the present study, administration of BSB, including atenolol, restored the nocturnal drop of LF/HF ratio. The prognostic influence of BSB in CKD patients who do not have left ventricular dysfunction should be further investigated.

We evaluated the effects of BSB and ABB (vasodilating) on cardiac autonomic function using HRV in the present study. There was no significant difference between BSB and ABB on HR in either Group-KD or Group-NKD.

In Group-NKD, BSB was associated with higher HF and lower LF/HF ratio throughout the day, and ABB was associated with higher day-time HF and lower night-time LF/HF ratio. This means that both BSB and ABB might augment parasympathetic activity and decrease sympathovagal balance.

In contrast, BSB and ABB had different effects on cardiac autonomic function in kidney dysfunction patients. BSB was associated with higher parasympathetic activity and lower sympathovagal balance in Group-KD; however,

ABB did not result in HF, LF, and LF/HF ratio differences in this patient population.

Our present study data suggest that the operative mechanisms of β -blockers and ABB, especially on cardiac autonomic function, are different depending on the presence of kidney dysfunction in patients without severe heart failure.

Carvedilol has been reported to attenuate oxidative stress.²⁷ In CKD patients without heart failure, carvedilol may express antioxidative effects to the fore rather than its ABB effect. In the present study, HR and LF/HF ratio of CKD patients were significantly reduced by BSB but not by ABB. Endothelial dysfunction and increased oxidative stress can be detected in early-stage CKD.²⁸ Zepeda, *et al.* reported that carvedilol increased endothelial antioxidant capacity.²⁷ If the antioxidative effect of ABB can attenuate endothelial dysfunction in CKD, then the relative vasodilation effect of ABB may explain the non-significant, night-time HR and LF/HF ratio reductions in CKD patients under ABB therapy (Figures A, D). This hypothesis should be further investigated using animal studies along with prospective and controlled human studies. The clarification may lead to a different indication for carvedilol therapy in this patient population.

Moreover, a recent study indicates the central nervous system acts on autonomic systems via oxidative stress.²⁹ Further investigations regarding the effect on the central nervous system, which may be exacerbated by CKD, should be conducted.

Limitations: Due to a retrospective single center study, the selection and the dose of BSB and ABB were not unified in the cohort. An overall higher dose of ABB may increase HF activity and decrease the LF/HF ratio further. Secondly, this is not a randomized study and not a paired design comparing same patients before and after β -

blockers use. The study design had two groups with different ages, which can affect autonomic function and the effect of sympatholytic agents (Table I). To overcome these limitations, we consecutively enrolled patients and incorporated clinical parameters in the multivariable model. As shown in Figure A, the HR in patients treated with ABB demonstrated a similar decrease to those treated with BSB. Therefore, we believe our data is reasonable in the clinical setting. However, further larger and randomized studies should be conducted to investigate the relevance of our data.

Conclusion

The effect of sympatholytic therapy depends on the presence of CKD and whether BSB or ABB is used. In CKD patients without severe heart failure, β -selective β -blockers could be associated with higher parasympathetic activity and lower sympathovagal balance.

Disclosures

Conflicts of interest: None.

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