Int J Clin Exp Med 2018;11(10):11038-11046
www.ijcem.com /ISSN:1940-5901/IJCEM0073718

Original Article

Decreased heart rate variability is associated with declined renal function in hypertensive patients

Dufang Ma[1], Ping Jiang[2], Rong Yu[2], Yongcheng Wang[2], Xiao Li[1]

[1]*Department of Cardiology, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, P. R. China;* [2]*First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, P. R. China*

Received January 30, 2018; Accepted July 6, 2018; Epub October 15, 2018; Published October 30, 2018

Abstract: The aim of the study was to identify the association between heart rate variability (HRV) and renal function in hypertensive patients. A total of 195 nondiabetic hypertensive patients without evident renal impairment were included in the present cross-sectional observational study. HRV was assessed for the entire 24 hours, and biomarkers of renal function including serum levels of creatinine, urea nitrogen, uric acid, and estimated glomerular filtration rate (eGFR) were measured. Association between HRV and renal function parameters was identified by univariate correlation analysis, stepwise multivariate linear regression analysis and binary Logistic regression analysis. Patients with depressed HRV (SDNN < 100 ms) had higher serum levels of urea nitrogen, creatinine, and uric acid as well as decreased eGFR values compared with patients with normal HRV (SDNN ≥ 100 ms). After adjusting for compounding factors, only eGFR remained positively correlated with SDNN (beta = 0.534, P < 0.01). Moreover, eGFR is an independent variable predicting the presence of depressed HRV (OR = 0.959 [0.931, 0.989]) according to logistic analysis. Our results indicate that declined HRV parameter SDNN is associated with declined renal function in essential hypertension.

Keywords: Heart rate variability, renal dysfunction, hypertension, autonomic dysfunction, glomerular filtration rate, uric acid

Introduction

Renal damage is one of the leading target organs damaged by hypertension [1, 2]. Autonomic dysfunction characterized with increased sympathetic activity and sympathetic-parasympathetic imbalance is reported to be involved in diabetic nephropathy [3]. Relatively speaking, whether autonomic dysfunction is associated with hypertension-induced renal dysfunction has been less clear.

Heart rate variability (HRV) is a practical and convenient way to evaluate cardiac autonomic function using standard electrocardiographic monitoring. Suppressed HRV (SDNN < 100 ms) has been used as a marker of cardiac autonomic dysfunction and an independent prognostic factor of cardiovascular diseases [4]. Studies have demonstrated that HRV is a predictor of adverse renal outcomes in patients with non-dialysis and dialysis chronic kidney diseases [5, 6]. Similarly, in diabetic patients, studies have reported that decreased HRV is associated with increased albuminuria and lower estimated glomerular filtration rate (eGFR) at baseline, which predicted subsequently declined eGFR [7, 8]. However, there has been a paucity of studies on the association between HRV and renal function in essential hypertensive patients without evident renal impairment. In this study, we aim to determine the association between HRV and renal function in a cohort of 195 nondiabetic hypertensive patients without evident renal impairment.

Materials and methods

Study population

This was a cross sectional study. The total sample was consecutively recruited at Cardiology Department of Shandong University of Traditional Chinese Medicine from 2014 to 2017,

and composed of 195 patients with essential hypertension. Hypertension was diagnosed according to guidelines [9], defining as systolic BP (SBP) ≥ 140 or diastolic BP (DBP) ≥ 90 mmHg, and patients on anti-hypertensive treatment were also considered as hypertensive, regardless of their BP values. Exclusion criteria for the present analysis were: Patients with secondary hypertension, old or acute myocardial infarction, diabetes mellitus, acute and chronic heart failure, cancer, liver cirrhosis and/or failure, moderate-to-severe renal dysfunction (eGFR < 60 mL/min/1.73 m^2), narcotics abuse, thyroid disease, mental illness (depression, anxiety, schizophrenia and moderate to severe insomnia), sleep apnea hypopnea syndrome, history of gastrointestinal bleeding and acute renal injury (within 12 months), and recent history of use of nephrotoxic drugs or contrast agents (within 6 months). All of the patients gave informed consent to participate in this research project, which was approved by the Ethics Committee of Shandong University of Traditional Chinese Medicine.

Clinical parameters

As has been previously described, comprehensive demographic characteristics including sex, age, smoking, alcohol intake, past history of diseases, and medications before enrollment were investigated by a pre-designed and pretested questionnaire.

Body weight, BP, abdomen ultrasound and cardiac ultrasound were analyzed and recorded at the first day of hospitalization. Measurement of BP was performed after a 10 minute period of rest using an electronic sphygmomanometer (HEM-7071, OMRON Healthcare cooperation, China), and two BP readings were taken from both arms at 30 second intervals between 08:00 and 09:00 AM on the second morning after hospital admission. Simultaneously, fasting venous blood was drawn on the second morning after hospital admission for biochemical parameters including fasting plasma glucose, creatinine, urea nitrogen, uric acid, lipid profile, homocysteine, and thyroid hormone (Free T3 and T4). Samples were centrifuged and serum was separated within 30 minutes of collection and stored at -20°C until analyzed. The analyses were performed in the clinical biochemical laboratory in our hospital by AU5400 automated analyzer (Olympus, Tokyo, Japan), and reference ranges are those used by the laboratory. Serum urea nitrogen and uric acid levels were measured using uric acid enzymatic assay kits and urea nitrogen enzymatic assay kits (Beckman Coulter, Inc, Suzhou, China), and serum creatinine levels were measured using creatinine PAP FS (Diasys diagnostic system co., LTD, Shanghai, China). eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]:

	Serum creatinine (umol/L)	eGFR (mL/min/1.73 m^2)
Female	≤ 62	$GFR = 144 \times (Scr/62)^{-0.329} \times (0.993)^{Age}$
	> 62	$GFR = 144 \times (Scr/62)^{-1.209} \times (0.993)^{Age}$
Male	≤ 80	$GFR = 144 \times (Scr/80)^{-0.411} \times (0.993)^{Age}$
	> 80	$GFR = 144 \times (Scr/80)^{-1.209} \times (0.993)^{Age}$

Heart rate variability

Patients were given 24-hours for the ECG Holter recording. The recorders were applied between 9:00 and 11:00 AM on the second day after hospital admission, and patients were asked to follow as closely as possible their usual daily activities during each monitoring session. As described in our previous study [11], long tracings were recorded and independently analyzed by an experienced operator masked to patients' clinical status using a JincoMed Holter System (MIC-3H-3L, Jinco Medical Equipment Company, Beijing, China). HRV was assessed for the entire 24 hours in both the time- and frequency-domain analysis. After classifying the QRS morphology, the RR intervals were confirmed manually until no QRS sequence was incorrectly labeled. Traces were checked to ensure R-waves were adequately identified from artifacts and ectopic beats, and sequences with normal QRS characteristics were analyzed for HRV analysis. Time-domain HRV analysis parameters were 1) SDNN: standard deviation of all of the RR intervals between two normal QRS complexes; 2) RMSSD: root mean square successive difference between each value and the preceding value. Fast Fourier transformation was used to convert the different successive RR intervals in the frequency domain. Data were analyzed in 10-minute epochs throughout the 24 hours and the results from all epochs were averaged to form a composite spectrum. The amplitudes of the following frequency-domain HRV parameters were

Table 1. Clinical characteristics of patients with SDNN < 100 ms and SDNN ≥ 100 ms

	SDNN < 100 ms (n = 95)	SDNN ≥ 100 ms (n = 100)	p
Male/Female	47/48	40/60	0.197
Age (yeas)	68.19 ± 10.53	64.52 ± 10.74	0.017*
Body weight (Kg)	67.25 ± 10.06	67.94 ± 11.11	0.449
Heart rate (bpm)	73.24 ± 15.26	66.47 ± 10.52	< 0.001*
Systolic blood pressure (mmHg)	145.45 ± 13.69	140.55 ± 14.01	0.014*
Diastolic blood pressure (mmHg)	82.11 ± 11.03	79.92 ± 11.37	0.175
Left ventricular ejection fraction (%)	61.68 ± 9.65	66.22 ± 5.15	0.019*
Stable angina pectoris (Yes/No)	71/24	74/26	1.000
Stroke (Yes/No)	25/70	19/81	0.235
Smoking (Yes/No)	42/53	40/60	0.565
Alcohol intake (Yes/No)	51/44	44/56	0.198
Total cholesterol (mmol/L)	4.73 ± 1.12	4.79 ± 1.18	0.688
Triglycerides (mmol/L)	1.68 ± 1.04	1.51 ± 1.09	0.261
LDL-cholesterol (mmol/L)	2.81 ± 0.97	2.88 ± 0.90	0.569
HDL-cholesterol (mmol/L)	1.08 ± 0.26	1.20 ± 0.68	0.121
Fasting blood glucose (mmol/L)	5.86 ± 1.25	5.61 ± 0.99	0.122
Homocysteine (umol/L)	15.87 ± 6.87	13.07 ± 4.95	0.001*
Medications before enrollment			
Antiplatelet drugs (Yes/No)	61/34	62/38	0.768
β-Blockers (Yes/No)	36/59	33/67	0.549
ACEI or ARB (Yes/No)	39/56	51/49	0.196
Calcium channel blockers (Yes/No)	31/64	35/65	0.763
Diuretics (Yes/No)	35/60	34/66	0.765
Statins (Yes/No)	56/39	57/43	0.885

All values are given in mean ± SD. Continuous variables were compared using independent-sample student's t test. Categorical variables were compared using the Chi-square test. *P < 0.05 was considered significant.

measured: very low frequency (VLF, 0.0033-0.004 Hz), low frequency (LF, 0.04-0.25 Hz), high frequency (HF, 0.25-2.5 Hz), and total power (TP, 0-2.5 Hz).

Statistical analysis

Statistical analyses were performed as described previously [11]. For study purposes, differences in characteristics between participants with SDNN < 100 ms (suppressed HRV) and those with SDNN ≥ 100 ms (normal HRV) were compared using Students' T-test for continuous variables and Chi-square test for dichotomous variables. This cut-off for SDNN has been reported to be a marker of autonomic dysfunction and a predictor of mortality in patients after myocardial infarction [4, 12, 13]. Pearson's or Spearman's analyses were performed to identify the correlation between HRV parameters (SDNN, RMSSD, LF, HF and TP) and biomarkers of renal function (serum levels of creatinine, urea nitrogen, uric acid, and eGFR. According to the results of univariate correlation analysis, stepwise multivariate linear regression analysis (inclusion at 0.05 and exclusion at 0.01) was employed to find out the independent predictors of renal function parameters. Binary Logistic regression analysis was also performed to identify significant independent related factors for suppressed HRV. Possible compounding factors including clinical variables (age, sex, body weight, smoking, alcohol drinking), history of ischemic heart disease and stroke, heart rate, SBP and DBP, medical therapy (antiplatelet drugs, β-blockers, ACEI/ARB, calcium channel blockers, diuretics, and statins), laboratory parameters (fasting blood sugar, triglycerides, total cholesterol, LDL-C, HDL-C, homocysteine, Free T3 and T4) and eGFR were regarded as independent variables. Differences were considered significant at the two-sided P < 0.05. Analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Baseline population characteristics

Table 1 showed the comparison of characteristics between the 95 patients with suppressed HRV and the 100 patients with normal HRV as a cutoff of 100 ms for SDNN [4]. Relative to patients with normal HRV, those patients with

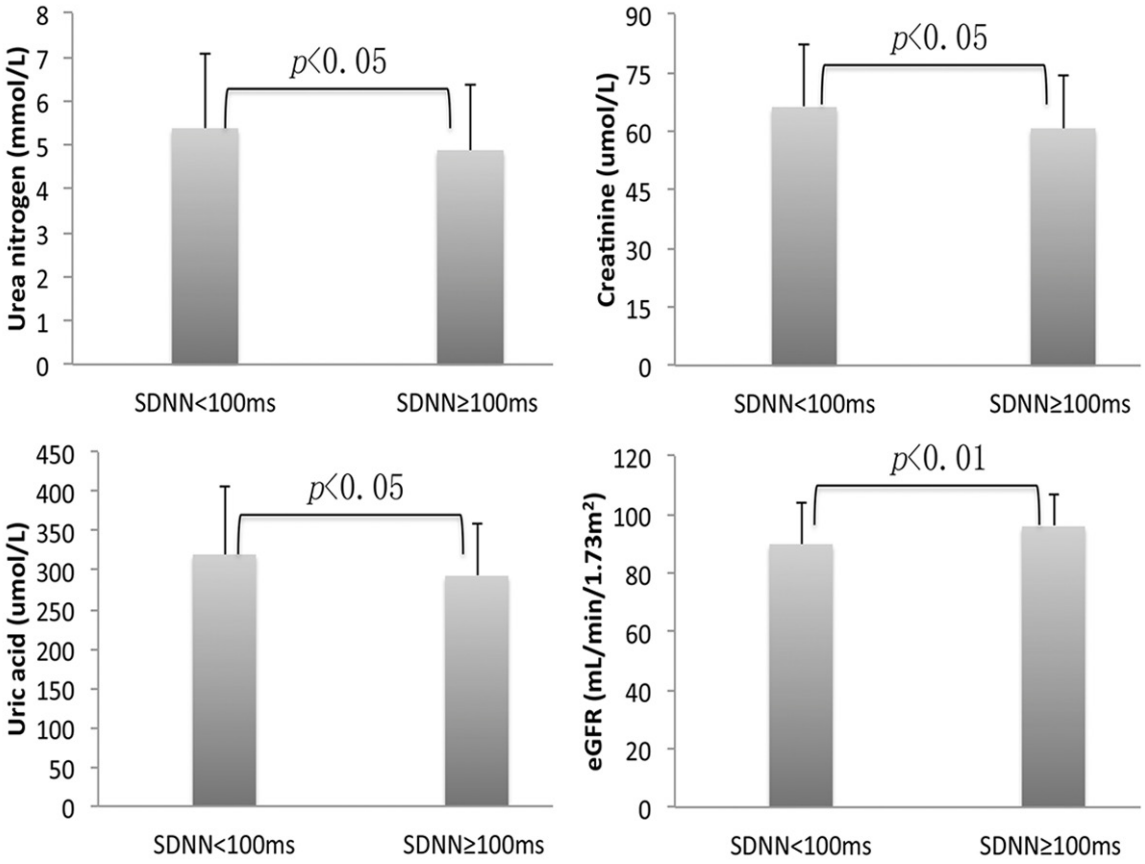

Figure 1. Biomarkers of renal function of patients with low HRV (SDNN < 100 ms) versus patients with normal HRV (SDNN ≥ 100 ms). Compared by use of independent- sample Student's T-test or the Mann-Whitney U test.

suppressed HRV were older (P < 0.05), and they had elevated SBP (P < 0.05), heart rate and serum levels of homocysteine (P < 0.01) and decreased left ventricular ejection fraction (P < 0.05).

Figure 1 shows the comparison of renal function parameters between the two groups. Compared with patients with normal HRV, patients with suppressed HRV had relatively increased blood levels of urea nitrogen (5.38 ± 1.68 vs. 4.88 ± 1.48 mmol/L, P < 0.05), creatinine (66.22 ± 16.27 vs. 60.77 ± 13.8 umol/L, P < 0.05) and uric acid (319.91 ± 86.79 vs. 292.79 ± 67.18 umol/L, P < 0.05). Moreover, those patients with suppressed HRV had lower values of eGFR than patients with normal HRV (89.87 ± 14.23 vs. 95.95 ± 11.12 mL/min/1.73 m^2, P < 0.01).

Relationship between HRV parameters and biomarkers of renal function

Table 2 shows univariate analyses between HRV parameters and biomarkers of renal function. SDNN were inversely correlated with blood levels of urea nitrogen, creatinine and uric acid (P < 0.01), while positively correlated with eGFR (P < 0.01). No relationship was found between RMSSD and any the renal function parameters. In addition, Spearman's analyses show that HRV frequency-domain parameter LF was positively correlated with eGFR (P < 0.05), and HF (P < 0.01) and TP (P < 0.05) were inversely correlated with blood levels of creatinine.

After adjusting possible confounding factors including clinical variables (age, sex, smoking, body weight, alcohol drinking), history of ischemic heart disease, stroke, heart rate, SBP and DBP, medical therapy (Antiplatelet drugs, β-blockers, ACEI/ARB, Calcium channel blockers, Diuretics and statins), laboratory parameters (blood fasting sugar, triglycerides, total cholesterol, LDL-C, HDL-C, homocysteine, Free T3 and T4), multiple linear regression analysis and logistic regression analysis were performed. As shown in **Table 3**, positive associations between eGFR and SDNN remained sta-

Table 2. Pearson's and Spearman's correlation analysis between HRV index and renal function parameters

	Urea nitrogen (mmol/L)		Creatinine (umol/L)		Uric acid (umol/L)		eGFR (mL/min/1.73 m^2)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SDNN	-0.246	0.001	-0.339	< 0.001	-0.224	0.002	0.273	< 0.001
RMSSD	-0.027	0.710	-0.100	0.165	-0.066	0.363	0.065	0.366
LF	-0.020	0.782	-0.128	0.079	-0.005	0.951	0.172	0.018
HF	-0.043	0.560	-0.194	0.008	-0.072	0.325	0.105	0.151
TP	0.054	0.567	-0.165	0.023	-0.085	0.241	0.142	0.050

Pearson's analyses were performed between SDNN and RMSSD and renal function parameters; Spearman's analyses were performed between LF, HF and TP and renal function parameters.

Table 3. Multivariate analysis of factors associated with SDNN in total sample

Independent variable	Dependent predictors	Unstandardized coefficient		Standardized coefficient (beta)	*p*
		B	SE		
SDNN	Heart rate	-0.748	0.180	-0.297	< 0.001
	Gender	-17.915	4.704	-0.283	< 0.001
	SBP	-0.589	0.164	-0.260	0.001
	eGFR	0.534	0.171	0.223	0.002
	HDL-C	22.407	9.193	0.176	0.016

Clinical variables (age, sex, body weight, smoking, alcohol drinking), history of ischemic heart disease and stroke, heart rate, SBP and DBP, medical therapy (antiplatelet drugs, β-blockers, ACEI/ARB, calcium channel blockers, diuretics and statins), laboratory parameters (urea nitrogen, uric acid, fasting blood sugar, triglycerides, total cholesterol, LDL-C, HDL-C, homocysteine, Free T3 and T4) and eGFR were regarded as independent variables.

tistically significant (beta = 0.534, P < 0.01). Moreover, SDNN was also associated with heart rate, gender, SBP and blood levels of HDL-C.

Consistent with the results of multiple linear regression analysis, binary logistic regression analysis revealed that increased blood levels of uric acid (OR = 1.006 [1.001, 1.011]) and decreased eGFR (OR = 0.959 [0.931, 0.989]) were independent variables relating the suppressed HRV (**Table 4**).

Discussion

Recently, a large cross-study comprised 9600 non-diabetic, never-treated hypertension individuals has demonstrated an association between the coefficient of variation of heart rate (Cv = standard deviation × 100/mean value) and declined renal function [14]. In agreement with this result, our present study showed a robust inverse association between time-domain HRV parameters SDNN and eGFR in 195 hypertensive patients without evident renal injury. Together with the results of prior results, these findings make it clear that decreased autonomic modulation is indeed related to the declined renal function in essential-hypertension patients.

Although both the renal injury and autonomic dysfunction are complications of hypertension, the complex interaction and cause-and-effect relationship between them is scanty and perplexing in the process of essential hypertension. Theoretically, renal sympathetic nerve terminals directly contact with renal vasculature and renal tubules [15], and modulate renal hemodynamics, tubular transport and renin secretion [16]. Indeed, a clinical study has indicated that pure autonomic dysfunction contributed to elevated serum levels of creatinine and urea nitrogen and decreased eGFR compared with patients without autonomic failure [17]. In the development of hypertension, it has been demonstrated that sympathetic activity is already increased at earlier stages when renal function is not or only slightly impaired in hypertension [18]. Prolonged sympathetic hyperactivity can induce changes in intrarenal blood vessels by releasing catecholamines, which induce proliferation of smooth muscle cells and adventitial fibroblasts in the renal vascular wall [19, 20]. Additionally, renal sympathetic overactivity leads to renal dysfunction through affecting filtration, secretion and reabsorption function [15, 21, 22]. With development of

Table 4. Binary logistic regression analysis results of the possible correlates for depressed HRV

	B	SE	OR	95% CI		*p*
				Lower	Upper	
Heart rate	0.052	0.018	1.053	1.017	1.090	0.003
SBP	0.031	0.014	1.031	1.003	1.060	0.028
Uric acid	0.006	0.002	1.006	1.001	1.011	0.011
eGFR	-0.041	0.016	0.959	0.931	0.989	0.008
Fasting blood glucose	0.347	0.169	0.040	1.415	1.016	0.040

Clinical variables (age, sex, body weight, smoking, alcohol drinking), history of ischemic heart disease and stroke, heart rate, SBP and DBP, medical therapy (antiplatelet drugs, β-blockers, ACEI/ARB, calcium channel blockers, diuretics and statins), laboratory parameters (urea nitrogen, uric acid, fasting blood sugar, triglycerides, total cholesterol, LDL-C, HDL-C, homocysteine, Free T3 and T4) and eGFR were regarded as independent variables.

hypertension, the impaired kidney progressively exacerbates sympathetic excitation through increasing sodium retention and hypervolemia and activating the renin-angiotensin -aldosterone system, which in turn result in elevated BP [23-25]. Thus, autonomic dysfunction characterized by sympathetic over-excitation may be an important underlying mechanism of hypertension-induced renal dysfunction.

HRV is determined by a complex interaction of sympathetic and parasympathetic activity. Decreased HRV is associated with autonomic dysfunction and a host of adverse outcomes in cardiovascular diseases and chronic kidney disease [26-28]. SDNN is the main parameter of time-domain analysis; it reflects the total modulation of both parasympathetic and sympathetic nerve system, and a suppressed SDNN value (SDNN < 100 ms) usually indicates relative sympathetic dominance and inhibited parasympathetic activity [13, 29]. RMSSD and HF predominantly reflect parasympathetic modulation, while LF and LF/HF represent sympathetic-parasympathetic balance. Moreover, LF has been variably though to represent sympathetic activity by some reports [5, 30].

In clinical practice, GFR is considered the best overall index of kidney function in health and disease. In the present study, we used CKD-EPI equation to estimate the values of GFR, which is applicable to a variety of populations and clinical conditions, and improves the bias at higher levels of estimated GFR [10]. Additionally, the blood levels of urea nitrogen, creatinine and uric acid are always considered as the markers of renal function, as they reflect the tubular reabsorption function and glomerular filtration function. In the present study, we found that hypertensive patients with depressed HRV had lower eGFR and higher blood levels of urea nitrogen, creatinine and uric acid when compared with patients with normal HRV. The results of univariate correlation analyses showed that SDNN was positively correlated with eGFR and inversely correlated with blood levels of urea nitrogen, creatinine, and uric acid. After adjusting the compounding factors, only eGFR remained positively correlated with SDNN. Moreover, eGFR is an independent variable predicting the presence of depressed HRV according to the logistic analysis. The present study was consistent with the retrospective analysis on a cohort of 200 hypertensive patients performed by Paolo et al. [31]. In his study, it was shown that LF/HF, a marker of sympatho-vagal balance, was significantly decreased in the groups with mild and moderate decreased eGFR, suggesting the involvement of autonomic imbalance in hypertension-related renal dysfunction. Similarly, studies performed in patients with chronic kidney diseases also suggested that lower frequency-domain HRV parameters were associated with higher risk of progression to end-stage renal diseases [26, 32]. These results powerfully supported that autonomic dysfunction is closely related to decreased renal function, or even renal damage.

High uric acid levels have been associated with decreased renal perfusion and tubular secretion of uric acid [33]. Another study has reported that increased blood levels of uric acid were related with an accelerated progression of hypertension and development of end-organ injury [34]. In the present study, elevated uric acid levels were found to be associated with the presence of depressed HRV according to the results of logistic analysis. Consistently, in pre-hypertensive patients, it has been demonstrated that uric acid inversely correlated with HRV parameters LF, suggesting uric acid is associated with sympathetic activity [35]. Nevertheless, the plausible mechanisms by which uric acid correlated with HRV parameters are not clearly known, it might be partly attrib-

uted to the increased sympathetic activity, because study has demonstrated that sympathetic over-activity in hypertension decreased renal clearance of uric acid, leading to elevated plasma levels of uric acid [16].

Limitations

There are limitations that should be acknowledged. First, the serum levels of uric acid, creatinine and urea nitrogen were obtained at a single time-point. In order to reduce the fluctuations, further study should measure these biomarkers at several different time-point. Second, this is an observational study and any associations between HRV parameters and renal function parameters did not definitely prove causality. Nevertheless, this study elucidated that adverse HRV parameters are associated with declined renal function. Longitudinal analysis of hypertensive patients will determine possible early predictive value of HRV on hypertension-induced renal dysfunction.

Conclusion

In conclusion, using a simple, cheap and non-invasive autonomic test, we have demonstrated that autonomic dysfunction is associated with declined renal function in essential hypertension. This finding may be helpful to early detect and diagnose hypertension nephropathy. Further research is needed to clarify the underlying mechanisms between autonomic dysfunction and decreased renal function in hypertension.

Acknowledgements

This study was supported in part by Chinese National Natural Science Foundation (No. 81673970) and the First-class Subject Funded Projects of Shandong Province (No. 220306). We thank all our colleagues working in the Electrocardiogram Room and Clinical Biochemistry Room, Affiliated Hospital of Traditional Chinese Medicine. This study was approved by the ethics committee of Shandong University of Traditional Chinese Medicine. A written informed consent was obtained from all the patients at the time of admission, with which the blood was authorized to scientific purpose.

Disclosure of conflict of interest

None.

Address correspondence to: Xiao Li, Department of Cardiology, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, 42 Wenhua Road, Jinan 250011, Shandong, P. R. China. Tel: +86-18753151199; E-mail: lixiao617@hotmail.com

References

[1] Kim MJ, Lim NK, Park HY. Relationship between prehypertension and chronic kidney disease in middle-aged people in Korea: the Korean genome and epidemiology study. BMC Public Health 2012; 12: 960.

[2] Seccia TM, Caroccia B, Calo LA. Hypertensive nephropathy. Moving from classic to emerging pathogenetic mechanisms. J Hypertension 2017; 35: 205-212.

[3] Yun JS, Ahn YB, Song KH, Yoo KD, Kim HW, Park YM, Ko SH. The association between abnormal heart rate variability and new onset of chronic kidney disease in patients with type 2 diabetes: a ten-year follow-up study. Diabetes Res Clin Pract 2015; 108: 31-37.

[4] von Kanel R, Carney RM, Zhao S, Whooley MA. Heart rate variability and biomarkers of systemic inflammation in patients with stable coronary heart disease: findings from the Heart and Soul Study. Clin Res Cardiol 2011; 100: 241-247.

[5] Chandra P, Sands RL, Gillespie BW, Levin NW, Kotanko P, Kiser M, Finkelstein F, Hinderliter A, Pop-Busui R, Rajagopalan S, Saran R. Predictors of heart rate variability and its prognostic significance in chronic kidney disease. Nephrol Dial Transplant 2012; 27: 700-709.

[6] Kurata C, Uehara A, Sugi T, Ishikawa A, Fujita K, Yonemura K, Hishida A, Ishikawa K, Tawarahara K, Shouda S, Mikami T. Cardiac autonomic neuropathy in patients with chronic renal failure on hemodialysis. Nephron 2000; 84: 312-319.

[7] Tahrani AA, Dubb K, Raymond NT, Begum S, Altaf QA, Sadiqi H, Piya MK, Stevens MJ. Cardiac autonomic neuropathy predicts renal function decline in patients with type 2 diabetes: a cohort study. Diabetologia 2014; 57: 1249-1256.

[8] Cho YH, Craig ME, Davis EA, Cotterill AM, Couper JJ, Cameron FJ, Benitez-Aguirre PZ, Dalton RN, Dunger DB, Jones TW, Donaghue KC; Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial. Cardiac autonomic dysfunction is associated with high-risk albumin-to-creatinine ratio in young adolescents with type 1 diabetes in AdDIT (adolescent type 1 diabetes cardio-renal interventional trial). Diabetes Care 2015; 38: 676-681.

[9] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty

AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A; European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28: 1462-1536.

[10] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604-612.

[11] Dufang M, Yongcheng W, Ping J, Yonghui Y, Xiao L. N-Terminal Pro-B-Type natriuretic peptide levels inversely correlated with heart rate variability in patients with unstable angina pectoris. Int Heart J 2016; 57: 292-298.

[12] Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm J. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. Am J Cardiol 1991; 68: 434-439.

[13] Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256-262.

[14] Liakos CI, Karpanou EA, Markou MI, Grassos CA, Vyssoulis GP. Correlation of 24-Hour blood pressure and heart rate variability to renal function parameters in hypertensive patients. The effect of smoking. J Clin Hypertens 2015; 17: 938-943.

[15] DiBona GF. Physiology in perspective: the wisdom of the body. Neural control of the kidney. Am J Physiol Regul integr Comp Physiol 2005; 289: R633-641.

[16] Joles JA, Koomans HA. Causes and consequences of increased sympathetic activity in renal disease. Hypertension 2004; 43: 699-706.

[17] Garland EM, Gamboa A, Okamoto L, Raj SR, Black BK, Davis TL, Biaggioni I, Robertson D. Renal impairment of pure autonomic failure. Hypertension 2009; 54: 1057-1061.

[18] Klein IH, Ligtenberg G, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic activity is increased in polycystic kidney disease and is associated with hypertension. J Am Soc Nephrol 2001; 12: 2427-2433.

[19] Erami C, Zhang H, Ho JG, French DM, Faber JE. Alpha(1)-adrenoceptor stimulation directly induces growth of vascular wall in vivo. Am J Physiol Heart Circ Physiol 2002; 283: H1577-1587.

[20] Zhang H, Faber JE. Trophic effect of norepinephrine on arterial intima-media and adventitia is augmented by injury and mediated by different alpha1-adrenoceptor subtypes. Circ Res 2001; 89: 815-822.

[21] Spallone V, Gambardella S, Maiello MR, Barini A, Frontoni S, Menzinger G. Relationship between autonomic neuropathy, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients. Diabetes Care 1994; 17: 578-584.

[22] Winocour PH, Dhar H, Anderson DC. The relationship between autonomic neuropathy and urinary sodium and albumin excretion in insulin-treated diabetics. Diabe Med 1986; 3: 436-440.

[23] Abdulla MH, Johns EJ. The innervation of the kidney in renal injury and inflammation: a cause and consequence of deranged cardiovascular control. Acta Physiol (Oxf) 2017; 220: 404-416.

[24] Esler M. The sympathetic nervous system in hypertension: back to the future? Curr Hypertens Rep 2015; 17: 11.

[25] Barrett CJ. Renal sympathetic nerves - what have they got to do with cardiovascular disease? Exp Physiol 2015; 100: 359-365.

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

[27] Binkley PF. Promise of a new role for heart rate variability in the clinical management of patients with heart failure. JACC Heart Fail 2017; 5: 432-434.

[28] Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol 2005; 10: 88-101.

[29] Heart rate variability. Standards of measurement, physiological interpretation and clinical use. Task force of the European society of cardiology and the North American society of pacing and electrophysiology. Eur Heart J 1996; 17: 354-81.

[30] Cygankiewicz I, Zareba W. Heart rate variability. Handb Clin Neurol 2013; 117: 379-393.

[31] Melillo P, Izzo R, De Luca N, Pecchia L. Heart rate variability and target organ damage in hypertensive patients. BMC Cardiovasc Disord 2012; 12: 105.

[32] de Oliveira CA, de Brito Junior HL, Bastos MG, de Oliveira FG, Casali TG, Bignoto TC, Fernandes NM, Beraldo AF, de Paula RB. Depressed cardiac autonomic modulation in pa-

tients with chronic kidney disease. J Bras Nefrol 2014; 36: 155-162.
[33] Perlstein TS, Gumieniak O, Williams GH, Sparrow D, Vokonas PS, Gaziano M, Weiss ST, Litonjua AA. Uric acid and the development of hypertension: the normative aging study. Hypertension 2006; 48: 1031-1036.
[34] Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002; 282: F991-997.
[35] Kunikullaya KU, Purushottam N, Prakash V, Mohan S, Chinnaswamy R. Correlation of serum uric acid with heart rate variability in hypertension. Hipertens Riesgo Vasc 2015; 32: 133-141.