Renal Function, Cardiovascular Risks, and Heart Rate Variability in the Elderly with Prehypertension and Hypertension from Eastern Thailand: A Preliminary Cross-Sectional Study

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Abstract

Data from biochemical and physiological investigations in prehypertension (PreHTN) individuals is essential to understanding the pathophysiologic mechanisms that cause progression from PreHTN to the hypertension (HTN) stage. This study investigated renal function, cardiovascular risks, and heart rate variability (HRV) in the elderly with PreHTN and HTN. Ninety-nine elderly subjects with PreHTN (n = 49) and HTN (n = 50) from Eastern Thailand were evaluated with respect to their renal function, cardiovascular risks (plasma glucose, serum high-sensitive C-reactive protein, serum lipid profile, and atherosclerogenic index [AI]), and HRV. After 12 hour overnight fasting, serum creatinine concentration was lower and estimated glomerular filtration rate was higher in the PreHTN group compared to those in the HTN group ($P < 0.05$). Plasma glucose concentration was lower, but serum total cholesterol (TC) and low-density lipoprotein (LDL)-cholesterol concentrations and AI were higher in the PreHTN group compared to those in the HTN group ($P < 0.05$). HRV parameters were not significantly different between PreHTN and HTN groups. The results of this study showed that elderly persons with PreHTN had higher renal function than those with HTN. Nevertheless, they may be at risk for cardiovascular disease due to high serum TC and LDL-cholesterol concentrations.

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Introduction

Hypertension (HTN) is quantitatively the most important risk factor for premature cardiovascular disease and contributes to extensive morbidity and mortality worldwide.[1] Prevalence of HTN is rising in low- and middle-income countries.[2] In Thailand, it is estimated that 11.5 million people are affected. HTN is associated with increased risks for cardiovascular disease (CVD) and chronic kidney disease (CKD).[2] Frequent cardiovascular complications include myocardial infarction, stroke, and congestive heart failure.[3] The causes of HTN are complex and mostly unknown. Secondary causes include elevated aldosterone, obstructive sleep apnea, renovascular disease, increased sympathetic activation, inflammation, and aging.[1]

Prehypertension (PreHTN) refers to the levels of blood pressure (BP) above normal but below HTN, that is 120-139/80-89 mmHg.[4] It was reported in 2010 that the prevalence of PreHTN in Thailand was 31.8%.[5] This number is similar to that of The National Health and Nutrition Examination Survey (NHANES), conducted from 1999-2006, which found that the prevalence of PreHTN in disease-free adults was 36.3% worldwide.[6] It has also been reported that 50% of individuals with PreHTN can progress to HTN within 5 years.[7] In addition to BP, data from biochemical and physiological investigations including renal function, cardiovascular risks, and heart rate variability (HRV) in PreHTN individuals are essential to understand the pathophysiologic mechanisms that cause progression from PreHTN to the HTN stage, particularly in the elderly. This preliminary study aimed to investigate biochemical and physiological parameters including renal function, cardiovascular risks, and HRV in the elderly with PreHTN and HTN from Eastern Thailand and also to determine the correlations among these parameters in each group.

Materials and Methods

Study population

This preliminary cross-sectional study was carried out in Mueang Chonburi District, Chonburi Province, Thailand, between June 2016 and March 2017. A total of 99 elderly subjects, 23 men and 76 women,

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aged 60-80 years, were recruited. Subjects were categorized into two groups according to their BP and self-reported treatment: PreHTN group (n = 49; age 66.90 ± 5.50 yr; body mass index, BMI, 23.84 ± 3.69 kg/m^2) and HTN group (n = 50; age 71.32 ± 5.99 yr; BMI 24.93 ± 4.69 kg/m^2). PreHTN and HTN were defined using 2013 ESH/ESC guideline:[8] PreHTN or high normal BP, systolic BP (SBP) 130-139 mmHg and/or diastolic BP (DBP) 85-89 mmHg; HTN, SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. BP was measured in the morning for 2 visits at the laboratory, 1 week apart. A heath questionnaire form was used to assess subjects' medical history, including underlying diseases, drugs treatment, and history of illness. A subject with PreHTN BP who had a prior history, diagnosis, or treatment of HTN would be classified as HTN. In HTN group, 7 subjects were newly diagnosed and had not received any BP-lowering medications, and 43 were on treatment. Thirty subjects reached their target BP while 13 subjects were refractory.

In addition to the heath questionnaire form, all subjects were assessed with Thai General Health Questionnaire-12 Form (also for mental health assessment) and physical examination, including vital signs (BP and heart rate, HR). To avoid confounding factors and ensure that results mainly arose from the effect of high BP, subjects who regularly smoked or drank, or had diabetes mellitus, thyroid disease, cardiovascular disease or renal disease were excluded. Subjects with dyslipidemia or on lipid-lowering medications were included because these conditions are commonly established in PreHTN and HTN.[9]

Ethics statement

All subjects were informed of their role in the study, both verbally and in writing. The consent form and study protocol were approved by the Human Ethics Committee, Burapha University (61/2559 and 197/2559) and the 1964 Helsinki declaration with later amendments.

Anthropometric assessment

Height and body mass were measured (Health O meter Pro Series, USA), and BMI was then calculated as mass/height^2 (kg/m^2). Body composition was measured in the standing position using a body fat monitor scale (Tanita UM076, Tokyo, Japan) based on bioelectrical impedance analysis. Fat distribution was assessed by waist-hip circumference ratio. Waist circumference was measured at the end of a normal expiration and at the mid-point between the bottom rib and the superior iliac spine. Hip circumference was measured on a horizontal plane at the level of maximum buttock extension. Body temperature was also determined using a digital thermometer (Microlife MT510, Widnau, Switzerland).

Assessments of BP and HR

In the morning, after 12-hour overnight fasting and refraining from medications, the subject's BP and HR were assessed in the supine position after resting for 15 minutes, using a digital automatic BP monitor (Microlife BP 3AQ1, Widnau, Switzerland). The BP cuff was closely wrapped around each subject's arm; The cuff lower edge was about 1 inch above the bend of elbow. BP and HR were assessed 3 times, 5 minutes apart and the average of the three readings was reported. Pulse pressure (PP), mean arterial pressure (MAP), and rate-pressure product (RPP) were calculated from the mean SBP and DBP.

Assessment of HRV

Following the BP and HR assessments, lead II electrocardiogram was obtained for 10 min in the supine position, using PowerLab 4/30 (ADInstruments, Sydney, Australia). Previous studies showed that short-term HRV analysis for 5-10 minutes was sufficient to determine cardiac autonomic function in subjects with HTN or PreHTN.[10,11] HRV analysis on the same equipment (PowerLab) consisted of time and frequency domains. The time domain comprised the standard deviation of normal beat-to-beat (R-R) intervals (SDNN) and the root-mean-square of successive R-R (RMSSD). In the frequency domain, the analysis comprised total power (TP), very low, low, and high frequency powers (VLF, DC to 0.04 Hz; LF, 0.04 to 0.15 Hz; and HF: 0.15 to 0.4 Hz), and LF/HF ratio.

Assessment of renal function

Glomerular filtration rate (GFR, m/min per 1.73 m^2) was estimated from serum creatinine concentration and age, using the equations from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI):[12]

Female, serum creatinine (Scr) ≤ 0.7 mg/dl:

$$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$$

Female, Scr > 0.7 mg/dl:

$$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$$

Males, Scr ≤ 0.9 mg/dl:

$$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$$

Males, Scr > 0.9 mg/dl:

$$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$$

Assessment of cardiovascular risks

In the morning, after 12-hour overnight fasting and refraining from medications, the subject's blood was drawn from an antecubital vein and collected in glucose and clot activator tubes. Analysis were performed within 2 hours for plasma glucose, high-sensitivity C-reactive protein (hsCRP), creatinine, and lipid profile (total cholesterol [TC], low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride [TG]).

These parameters are routinely assayed in the Medical Laboratory Unit, Burapha University Hospital. Plasma glucose concentration, and serum creatinine, TC, and TG concentrations were measured with enzymatic methods. Serum HDL-cholesterol concentration was measured with accelerator selective detergent method. LDL-cholesterol concentration was obtained by calculation. These parameters were

assayed using standard automated laboratory machine (Architect c8000, Abbott, Lake Bluff, Illinois, USA). Serum hsCRP concentration was measured with immunoturbidimetric method, also using automated equipment (Architect ci8200, Abbott). Atherosclerogenic index (AI), as an indicator for coronary heart disease and metabolic risks, was calculated from the following equation:[13,14,15]

AI = (TC - HDL-cholesterol) / HDL-cholesterol

Data analysis

All statistical analyses were performed with IBM SPSS Statistics version 21 (IBM Company, Chicago, Illinois, USA). Shapiro-Wilk test was used to assess data normal distribution. Chi-squared (χ^2) test was used to assess differences (for proportions) in gender and clinical chracteristics of subjects in Table 2. Student's *t*-test was used to assess differences (for mean) between PreHTN and HTN groups. Pearson correlation analysis was used to assess correlations among parameters, including BP and HR, renal function, cardiovascular risks, and HRV parameters in each group. All data were presented as mean ± SD. A P value < 0.05 was considered significant.

Results

Physical characteristics

The PreHTN group had significantly lower age than HTN group ($P < 0.05$). There were no significant differences between groups in gender, height, body mass, BMI, body fat percentage, fat mass, fat-free mass, body water percentage, water mass, visceral fat levels, and waist and hip circumferences and their ratio (Table 1).

Clinical characteristics

There were no significant differences in cigarette smoking and alcohol consumption behavior between PreHTN and HTN groups. However, history of having high serum lipids and receiving lipid-lowering medications was significantly higher in HTN group ($P < 0.05$; Table 2). Forty-three HTN subjects (86%) were receiving antihypertensives, namely, diuretics (6%), angiotensin-converting enzyme (ACE) inhibitors (18%), angiotensin receptor blockers (30%), beta blockers (10%), and calcium channel blockers (36%) (Table 2).

BP and HR

The PreHTN group had significantly lower SBP, PP, and MAP than HTN group ($P < 0.05$) (Table 3).

Correlation analyses in the PreHTN group showed no association between BP and HR with other parameters. In the HTN group, HR was associated with hsCRP ($r = 0.36$; $P < 0.05$).

HRV

There were no significant differences in HRV parameters, i.e., SDNN, RMSSD, TP, VLF, LF, HF, and LF/HF ratio, between PreHTN and HTN (Table 4).

Table 1 Physical characteristics of subjects.

	PreHTN (n = 49)	HTN (n = 50)	*P*
Age (yrs)	66.90 ± 5.50	71.32 ± 5.99	0.00
Gender (M/F) (%)	10/39 (20.4/79.6)	12/38 (24.0/76.0)	0.67
Height (m)	1.56 ± 0.08	1.56 ± 0.08	0.74
Body mass (kg)	58.08 ± 9.70	60.38 ± 11.79	0.29
BMI (kg/m^2)	23.84 ± 3.69	24.93 ± 4.69	0.20
Body fat (%)	31.61 ± 8.13	32.25 ± 9.46	0.72
Fat mass (kg)	18.64 ± 6.74	19.99 ± 8.51	0.38
Fat-free mass (%)	64.86 ± 7.93	63.72 ± 9.32	0.52
Fat-free mass (kg)	37.37 ± 6.39	37.91 ± 6.96	0.69
Body water (%)	50.09 ± 4.46	50.16 ± 5.77	0.94
Water mass (kg)	28.96 ± 4.91	29.98 ± 5.45	0.33
Viceral fat level	8.71 ± 3.78	9.92 ± 3.95	0.12
Waist (cm)	81.59 ± 10.74	83.54 ± 10.74	0.37
Hip (cm)	95.36 ± 8.60	97.16 ± 9.43	0.32
W/H ratio	0.85 ± 0.07	0.86 ± 0.07	0.74

Mean ± SD. PreHTN, prehypertension; HTN, hypertension; BMI, body mass index; Waist, waist circumference; Hip, hip circumference; W/H, waist-hip circumference ratio. $P < 0.05$, statistically significant difference between groups.

Table 2 Clinical characteristics of subjects.

	PreHTN (n = 49)	HTN (n = 50)	*P*
Cigarette smoking, n (%)	-	2 (4)	0.16
Alcohol consumption, n (%)	3 (6.12)	4 (8)	0.72
History of HTN, n (%)			
- Old cases	-	43 (86)	
- Newly diagnosed cases	-	7 (14)	
High serum lipids, n (%)	10 (20.41)	25 (50)	0.00
Medications, n (%)			
Lipid-lowering medications	8 (16.33)	19 (38)[a]	0.02
Antihypertensive medications[b]			
- Diuretics	-	3 (6)	
- ACE inhibitors	-	9 (18)	
- Angiotensin receptor blockers	-	15 (30)	
- Beta blockers	-	5 (10)	
- Calcium channel blockers	-	18 (36)	

Mean ± SD. [a]All subjects received lipid-lowering medication plus antihypertensive; [b]14 subjects (28%) received two antihypertensive medications; PreHTN, prehypertension; HTN, hypertension; ACE, angiotensin-converting enzyme. $P < 0.05$, statistically significant difference between groups.

Table 3 Blood pressure and heart rate of subjects.

	PreHTN (n = 49)	**HTN** (n = 50)	***P***
HR (beats/min)	63.47 ± 8.68	63.37 ± 10.45	0.96
SBP (mmHg)	127.12 ± 5.45	136.51 ± 15.35	0.00
DBP (mmHg)	73.81 ± 7.42	76.28 ± 8.79	0.20
PP (mmHg)	53.31 ± 5.95	60.23 ± 12.81	0.00
MAP (mmHg)	91.58 ± 6.22	96.36 ± 9.67	0.01
RPP (mmHg.bpm)	8392.82 ± 1295.04	8847.76 ± 1966.03	0.26

Mean ± SD. PreHTN, prehypertension; HTN, hypertension; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; RPP, rate-pressure product. $P < 0.05$, statistically significant difference between groups.

Table 4 Heart rate variability of subjects.

	PreHTN (n = 49)	HTN (n = 50)	*P*
SDNN (ms)	39.41 ± 16.23	41.35 ± 16.73	0.56
RMSSD (ms)	31.87 ± 21.99	37.94 ± 20.90	0.16
TP (ms^2)	1657.62 ± 1453.01	1860.24 ± 1443.75	0.49
VLF power (ms^2)	913.49 ± 1061.01	890.31 ± 914.72	0.91
LF power (ms^2)	265.88 ± 252.99	302.81 ± 289.80	0.50
LF power (nu)	41.65 ± 19.92	36.38 ± 19.45	0.19
HF power (ms^2)	398.20 ± 505.44	522.44 ± 573.74	0.26
HF power (nu)	47.43 ± 17.34	49.83 ± 17.84	0.50
LF/HF ratio	1.28 ± 1.40	1.10 ± 1.51	0.54

Mean ± SD. PreHTN, prehypertension; HTN, hypertension; SDNN, the standard deviation of normal beat-to-beat (R-R) intervals; RMSSD, the root-mean-square of successive R-R; TP,total power; VLF, very low frequency; LF, low frequency; HF, high frequency; nu, normalized unit.

Table 5 Cardiovascular risks and renal function of subjects.

	PreHTN (n = 49)	HTN (n = 50)	*P*
FG (mg/dl)	91.41 ± 10.76	96.10 ± 11.27	0.04
TG (mg/dl)	125.31 ± 65.11	114.94 ± 50.93	0.38
LDL-C (mg/dl)	137.47 ± 38.74	121.32 ± 36.74	0.04
HDL-C (mg/dl)	49.76 ± 11.16	50.08 ± 11.31	0.89
TC (mg/dl)	212.35 ± 41.40	194.42 ± 40.94	0.03
AI	3.46 ± 1.21	3.00 ± 0.95	0.04
hsCRP (mg/l)	2.54 ± 4.71	2.58 ± 4.13	0.97
Creatinine (mg/dl)	0.83 ± 0.16	0.93 ± 0.29	0.03
eGFR (ml/min/1.73 m^2)	79.73 ± 12.31	70.50 ± 16.79	0.00

Mean ± SD. PreHTN, prehypertension; HTN, hypertension; FG, fasting glucose; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TC, total cholesterol; AI, atherosclerogenic index; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate. $P < 0.05$, statistically significant difference between groups.

In the PreHTN group, there were correlations between HRV parameters and renal function, and between HRV parameters and cardiovascular risks ($P < 0.05$). SDNN was associated with eGFR and AI. RMSSD was associated with AI. TP and LF were associated with eGFR, while HF was associated with eGFR and TG. Note that TP was dominantly associated with eGFR ($r = 0.34$) and RMSSD was dominantly associated with AI ($r = -0.34$) in the PreHTN group (Table 6).

Similarly, in the HTN group, there were also correlations between HRV parameters and cardiovascular risks ($P < 0.05$). SDNN, TP, and VLF were associated with LDL-cholesterol and TC. LF was associated with hsCRP. HF was associated with HDL-cholesterol and hsCRP, whereas LF/HF ratio was associated with hsCRP. The results note that the LF/HF ratio was strongly associated with hsCRP ($r = 0.58$) in the HTN group (Table 6).

Renal function

The PreHTN group had a significantly lower serum creatinine level and higher eGFR than HTN group ($P < 0.05$) (Table 5).

In the PreHTN group, the correlations between eGFR and HRV parameters, namely, eGFR and SDNN, TP, LF, and HF ($P < 0.05$). Note that eGFR was dominantly associated with TP ($r = 0.34$) in the PreHTN group (Table 6). There were no associations between renal function and other parameters in the HTN group.

Cardiovascular risks

The PreHTN group had significantly lower plasma glucose concentration, and higher serum LDL-cholesterol and TC concentrations and AI than those of HTN group ($P < 0.05$). There were no significant differences in serum TG, HDL-cholesterol, and hsCRP concentrations between PreHTN and HTN groups (Table 5).

In the PreHTN group, the correlations between cardiovascular risks and HRV parameters include TG and HF, AI and SDNN, and AI and RMSSD ($P < 0.05$). Interestingly, AI was also correlated with hsCRP ($P < 0.05$). Again, AI was dominantly associated with RMSSD ($r = -0.34$; Table 6). There were no associations between cardiovascular risks

Table 6 Correlation coefficient between parameters of heart rate variability, renal function, and cardiovascular risks of subjects.

	SDNN (ms)	RMSSD (ms)	TP (ms^2)	VLF (ms^2)	LF (ms^2)	LF (nu.)	HF (ms^2)	HF (nu.)	LF/HF ratio
PreHTN									
eGFR	-0.26*	0.15	0.34*	-0.21	-0.24*	-0.00	0.23*	0.04	-0.03
TG	0.22	0.25	0.27	0.14	0.27	0.08	0.31*	0.10	-0.12
AI	0.31*	-0.34*	0.22	0.12	0.22	0.06	0.20	0.13	0.08
HTN									
LDL-C	-0.29*	0.22	-0.32*	0.31*	0.24	0.10	0.17	0.04	0.04
HDL-C	0.20	0.29	0.26	0.12	0.25	0.14	0.34*	0.13	0.04
TC	-0.28*	0.24	-0.34*	0.31*	0.26	0.08	0.21	0.06	0.01
hsCRP	0.08	0.16	0.03	0.01	0.38*	0.02	-0.33*	0.04	0.58*

PreHTN, prehypertension group; HTN, hypertension group; AI, atherosclerogenic index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol, TG, triglyceride. *$P < 0.05$.

and renal function in the PreHTN group.

In the HTN group, the correlations between cardiovascular risks and HR include hsCRP and HR ($P < 0.05$). The correlations between cardiovascular risks and HRV parameters include LDL-cholesterol and SDNN, LDL-cholesterol and TP, LDL-cholesterol and VLF, HDL-cholesterol and HF, TC and SDNN, TC and TP, TC and VLF, hsCRP and LF, hsCRP and HF, and hsCRP and LF/HF ratio ($P < 0.05$). Again, hsCRP was strongly associated with LF/HF ratio ($r = 0.58$) (Table 6). There were also no associations between cardiovascular risks and renal function in the HTN group.

Discussion

This preliminary study investigated renal function, cardiovascular risks, and HRV in the elderly with PreHTN and HTN from Eastern Thailand. The main results demonstrated that elderly persons with PreHTN had higher renal function, serum TC, and LDL-cholesterol levels than elderly with HTN. The results also demonstrated associations among parameters of renal function, cardiovascular risks, and HRV in both groups.

In this study, statistically significant differences between PreHTN and HTN subjects were observed in the parameters of renal function and cardiovascular risks. Plasma glucose in the PreHTN group was lower than that in the HTN group, which was consistent with results from other studies.[16,17] Previous reports also showed that HTN was related to increased risk for type 2 diabetes mellitus (T2DM) more than PreHTN at about 31%.[16] In addition, another previous study showed that, with the exception of HDL-cholesterol, the lipids were higher in HTN group when compared to those in the PreHTN group.[17] However, our study observed that TC and LDL-cholesterol levels, and also AI were lower in the HTN group. Subjects in both groups had a history of dyslipidemia and received lipid-lowering medications, e.g., atorvastatin and simvastatin. However, the percentage of subjects receiving lipid-lowering medications was significantly higher in HTN than PreHTN group (38.00% *vs* 16.33%; $P < 0.05$). Differences in drug dosages might also influence the results.[18] Thus, it is very likely that lipid-lowering medication in subjects of this study contributed to the lower TC and LDL-cholesterol levels in the HTN group and hence lower AI.

Although previous evidence indicated that hsCRP level was higher in HTN compared with PreHTN stage,[19] our results did not show any significant difference between groups in this parameter. Extensive clinical trial data have shown that lipid-lowering medications such as statins reduce hsCRP levels.[20] This may explain the absence of significant difference in hsCRP levels between groups. In addition, statins have been found to increase glycosylated hemoglobin and fasting serum glucose levels.[21] In this study, fasting blood glucose was significantly higher in HTN group, showing a potential adjacent effect of lipid-lowering medications on blood glucose. It has also been reported that thiazide diuretics and beta blockers elevated serum glucose concentrations.[22] Thus, the combined effect of lipid-lowering medications and antihypertensives, i.e., thiazide diuretics and beta blockers, might promote blood glucose elevation in HTN group.

This study showed correlations between cardiovascular risks and HRV parameters in both PreHTN and HTN groups, though mainly found in PreHTN. AI was negatively associated with RMSSD, which reflects parasympathetic function.[23] Previous studies reported that dysfunction of the autonomic nervous system (ANS), sympathetic and parasympathetic, has been identified as risk factors for atherosclerosis. The ANS regulates vascular wall contraction and tension and endothelial function via nitric oxide formation.[24] Hijmering et al. demonstrated that sympathetic stimulation impairs flow-mediated dilation response of vessels.[25] Moreover, decreased parasympathetic modulation was associated with worse early outcome in patients with acute large artery atherosclerotic infarction.[26] Furthermore, the ANS is thought to interact with other atherosclerotic risk factors in various ways, also affecting atherosclerotic process.[25] Our study also found a positive association between AI and hsCRP, a circulating acute-phase reactant that reflects active systemic inflammation.[27] Previous studies reported a positive association between hsCRP and evidence of atherosclerosis.[27,28] In the HTN group, hsCRP was positively associated with HR and LF/HF ratio. LF/HF ratio has been used to quantify the degree of sympathovagal balance.[29] Higher LF/HF ratio indicates higher sympathetic activity.[30] Our results are consistent with previous studies which found that hsCRP was positively correlated with LF/HF ratio.[31,32] Aso *et al*. demonstrated that high serum hsCRP concentrations are associated with relative cardiac sympathetic overactivity in patients with T2DM.[33]

Our study also showed that the PreHTN group had higher renal function than the HTN group. Serum creatinine concentration was higher and eGFR was lower in the HTN group. These results consorted with a study of Garofalo *et al*. conducted in a large population.[34] Their results also demonstrated that every 10 mmHg increase in SBP and DBP was associated with higher risk for decreased eGFR, particularly in older patients. It has been reported that HTN was a significant risk factor for incident CKD, while PreHTN was associated with a 20% increase in risk, which did not reach a significant level.[16,35] However, it is evident that the prevalence of CKD increased with BP and that PreHTN was also found to be an independent risk factor of CKD, particularly in men.[36] It is well established that the increased prevalence of CKD is a consequence of the accumulation of risk factors, such as HTN and

metabolic abnormalities including diabetes, dyslipidemia, and obesity.[36] Regardless of lipid profile and BMI, our subjects in the HTN group showed a higher SBP, PP, and MAP levels and plasma glucose concentration than those in the PreHTN. These factors could also lead to lower renal function in the HTN group. On the other hand, there has been evidence that lipid-lowering medications such as statins appear to protect the kidneys through cholesterol reduction and noncholesterol-mediated mechanisms. Clinical studies indicate that treatment with statins decelerate the deterioration of the GFR.[37]

Our study demonstrated correlations between renal function and HRV parameters in the PreHTN group. eGFR was positively associated with HF and TP. HF reflects cardiac parasympathetic nerve activity whereas TP reflects overall HRV.[38,39] Decreased HRV has been attributed to cardiac autonomic impairment and associated with increased risk of end-organ damage.[40,41] Liakos *et al.* reported a positive association between HRV and renal function including creatinine clearance and eGFR.[42] These data further suggested that reduced HRV may be associated with subtle alterations in renal function even in patients without overt kidney disease.

Our results did not demonstrate statistically significant differences in HRV parameters between PreHTN and HTN groups. HRV has proven to be the best tool to diagnose PreHTN at an early stage.[43] Reduced HRV was found in patients with systemic HTN, suggesting that autonomic dysfunction is present in the early stage of HTN.[44] Pal et al. observed that autonomic imbalance in PreHTN was due to increased sympathetic activity and decreased vagal activity, whereas in HTN, vagal inhibition was more prominent than sympathetic overactivity.[45,46] Ay *et al.* did not observe a significant difference in HRV parameters between patients previously treated for HTN and those newly diagnosed with HTN.[47] Another study has compared power distribution of HRV among different BP levels and found similarly higher LF power in PreHTN and HTN groups when compared to normotensive group.[48] In the present study, we did not investigate normotensive elderly. However, the previous studies showed that HRV is lower in mild or moderate untreated HTN.[49] In addition, adolescents with primary HTN had lower SDNN, RMSSD, pNN50, and HF power and higher LF power and LF/HF ratio compared to normal subjects.[50,51] These results suggest that there is sympathetic overactivity and vagal withdrawal in patients with PreHTN and HTN.

Antihypertensive medications that HTN group were receiving were diuretics (6%), ACE inhibitors (18%), angiotensin receptor blockers (30%), beta blockers (10%), and calcium channel blockers (36%). These drugs might have an effect on HRV results. A previous study reported that different classes of antihypertensive medications interfered differently with cardiac function and other systems. The main medications that have been clearly shown to affect sympathetic nervous system function are beta blockers, while the effects of ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics on sympathetic nervous system function remain controversial.[52] There is evidence that the combination of hydrochlorothiazide (a diuretic) plus bisoprolol (a beta blocker) reduced total and LF powers, increased HF power, and therefore decreased the LF/HF ratio.[53] The data indicate an increase in parasympathetic nervous system function after the drug administration. This evidence might partly explain our results which did not find a significant difference in HRV parameters between PreHTN and HTN groups, even though previous studies have shown that HRV in HTN was lower than in PreHTN.[11]

Our study has some limitations. First, this was a preliminary study. We studied a small population, and thus the results may not well represent PreHTN and HTN populations. Second, we did not investigate renal function, cardiovascular risks, and HRV in the elderly with normotension, thus precluding us from clarifying some essential results or comparing them with previous results. Finally, subjects in both groups were rather different in conditions. Most HTN subjects have had medical treatments, while PreHTN subjects were mostly new-found cases; hence some differences between PreHTN and HTN groups in this study could be due to the treatments.

On the other hand, to the best of our knowledge, this is the first study to investigate both biochemical and physiological parameters, including renal function, cardiovascular risks, and HRV in the elderly with PreHTN and HTN. Although the subjects in both groups were not equivalent in many aspects, we considered each confounding factor with regards to reports in the literature in an attempt to clarify the effects of high BP as well as medication on renal function, cardiovascular risks, and HRV. In addition, we also determined the associations among these parameters in both PreHTN and HTN groups. Even though most of them show weak relationship, our data may provide an understanding of relations between renal function, cardiovascular risks, and HRV in PreHTN and HTN.

Conclusion

The results from the present study indicate that elderly persons with PreHTN had higher renal function than that of elderly persons with HTN. Nevertheless, based on the data of high serum lipids (TC and LDL-cholesterol concentrations) and AI, it could be suggested that they may be at risk of cardiovascular disease. Thus, lifestyle modification is strongly recommended in these persons.

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Conflict of Interest

None to declare.

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