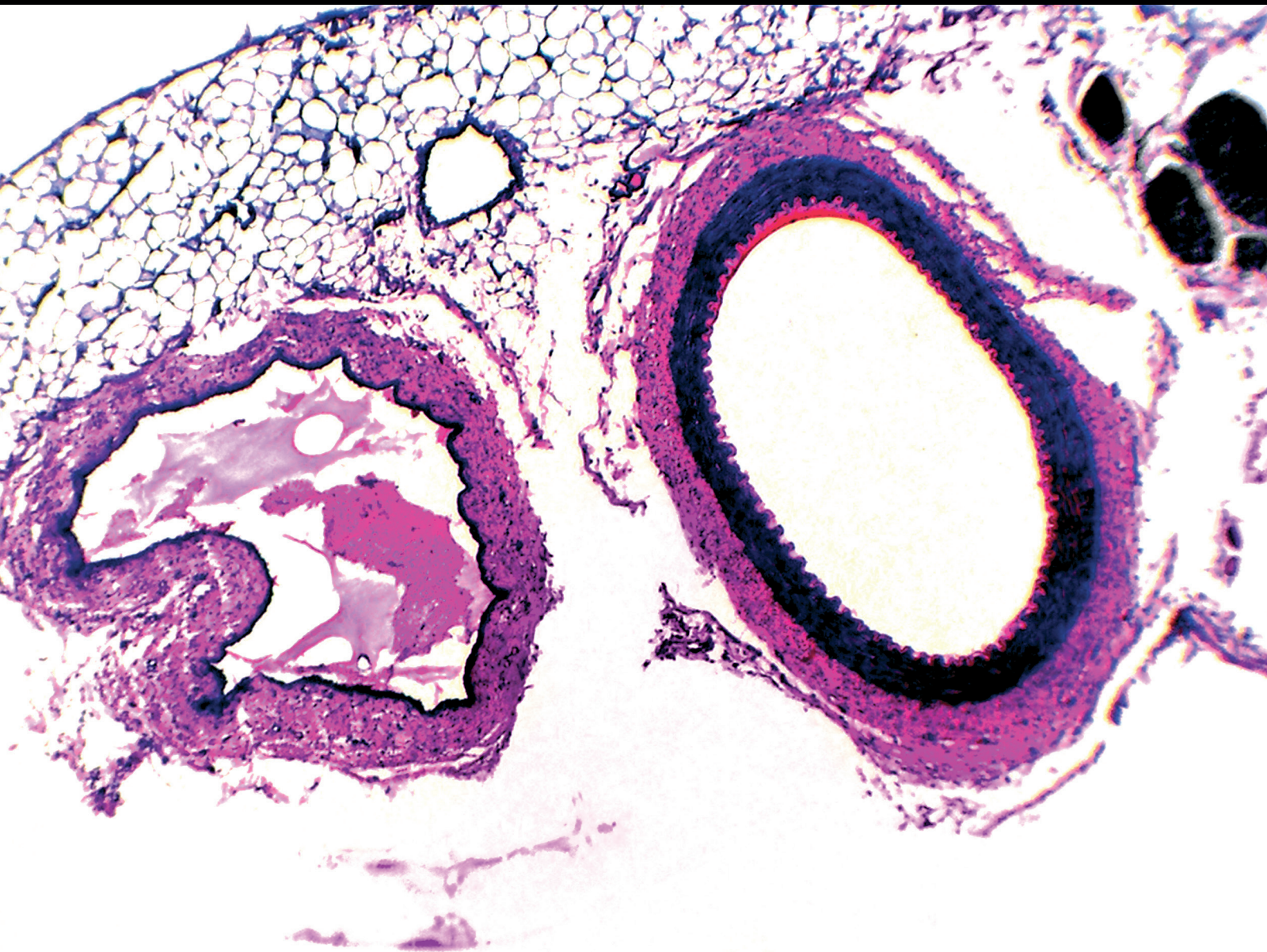# Prevalence and Challenges of Hypertensive Heart Diseases in the Real World

Lead Guest Editor: Kai Hu
Guest Editors: Chengxing Shen and Qin Yu

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Editorial Board

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Editorial

Prevalence and Challenges of Hypertensive Heart Diseases in the Real World

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Hypertension is the leading cause of global mortality and morbidity and remains the major and relatively easy preventable disease. However, investigation of prevalence and targeted efficient intervention of hypertensive heart diseases have been neglected in varying degrees over the past few years.

In this context, the studies of prevalence of hypertensive heart diseases and the potential of novel treatment and their challenges to combat and treat hypertensive heart diseases in the real world have attracted the interest of many scientists.

Liu et al. compared the prevalence of hypertension between the island and rural residents in Dalian, China. They performed modified MONICA questionnaire survey and found that prevalence of hypertension is extremely high in surveyed residents in island and rural areas of Dalian city. Moreover, awareness, treatment, and control rate of hypertension is much lower in surveyed residents than national level.

Coincidentally, Khader et al. used a multistage sampling technique to select a nationally representative sample of adults from the population of Jordan. They showed that almost one third of Jordanian adults suffer from hypertension. Dismayingly, there was nonsignificant decrease in hypertension prevalence over nearly one decade. However, it is important to note that the rate of hypertension awareness increased significantly among men and women.

Whilst Aya and Hussain investigated the trend in the prevalence of hypertension in Greater Beirut Area, they found it to be consistent and relatively high, yet there was an observed improvement in the awareness and control of the disease.

It is well documented that hyperactivity of the sympathetic nervous system contributes a pivotal role in the pathophysiology of hypertension. Heart rate variability (HRV) and heart rate turbulence (HRT) reflect the autonomic regulation of cardiac function. Yu et al. explored the relationship between blood pressure control and autonomic nervous function assessing by HRV and HRT in hypertensive patients and demonstrated that impaired autonomic nervous function in hypertensive patients.

Recent clinical studies have shown that there are some controversies on the efficacy of RDN (renal denervation) in the treatment of hypertension. In the study by Li et al., data clearly demonstrated that the new RDN system is safe and could effectively reduce blood pressure in hypertensive patients in the absence of antihypertensive medications.

When it comes to screening LVH (left ventricular hypertrophy) in population, echocardiography is the current "gold standard" yet not an appropriate method for public screening. Hence, Park and Chon explored the effectiveness of combination of cardiothoracic ratio (CTR) in chest X-ray and well-known risk factors besides electrocardiography in

asymptomatic hypertensive individuals. The authors showed that summing up the number of the risk factors of female, age $\geq$ 65 y, BMI $\geq$ 25 kg/m^2, SLVA $\geq$ 35 mm, and CTR $\geq$ 0.50 may be a better diagnostic tool for screening LVH than the electrocardiography-only criteria, at the score $\geq$ 2.

Besides essential hypertension, whether there are similar hemodynamic abnormalities that antedate the onset of fixed hypertension remains obscure. In the study by Ting et al., the answer is yes! This supports the notion that the elevation of blood pressure in hypertension may represent a later manifestation of an already abnormal vascular system rather than the vascular abnormalities being a result of the hypertension.

Risk factor profiles, clinical manifestations, and prognosis might differ between young patients with acute coronary syndrome (ACS) and elderly ACS patients. Ge et al. performed a retrospective and nonrandomized single center study and suggested that hypertension serves as an independent risk factor of multiple vessel disease and related to higher MACE rate during the short-term follow-up in young adults with ACS.

Although it is obvious from the studies included in this Special Issue that many advances have been made in clinical research highlighting the importance of improving the awareness of prevalence and taking effective and targeted intervention to combat the hypertensive heart disease in the real world, there are many grave issues still on the way, which need to be overcome. Firstly, the epidemiologic studies were performed in China, Jordan, and Lebanon, which were located in Asia, which cannot represent global status. Efforts should be launched to address the epidemiological surveys around the whole world. Secondly, although the awareness and control of hypertension have been promoted in the real world, the prevalence of this disease has not experienced a significant decrease or is even extremely high in surveyed area. Therefore, it is an urgent task for us to mount a comprehensive attack on hypertensive heart disease, harnessing all available resources to slow, arrest, and possibly even reverse the epidemic of hypertension.

Overall, the path ahead to mitigate the burden of hypertensive heart disease in real world is long and daunting, but watchful waiting is not an option. The progress reported in this Special Issue provides a relatively comprehensive prospect of hypertensive heart disease over the world highlighting the urgent task for us to take feasible strategies to effectively fight the hypertension and reduce the disease burden around the world.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this Special Issue.

Kai Hu
Chengxing Shen
Qin Yu

Research Article

A Comparison on Prevalence of Hypertension and Related Risk Factors between Island and Rural Residents of Dalian City, China

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This study aimed to compare the prevalence of hypertension between the island and rural residents in Dalian, China, and to explore associated risk factors of hypertension in order to provide evidence for the establishment of targeted strategy of hypertension prevention and treatment for island and rural residents. The modified MONICA questionnaire survey was performed on 7764 island and rural residents aged ≥40 years (including 2652 island residents and 5112 rural residents). Our data showed that totally weighted prevalence of hypertension was significantly higher in rural residents than in island residents (61.9% vs. 55.2%, P<0.001). Multivariate binary logistic regression analysis showed that older age, higher BMI, lower education level, and higher LDL-C and UA levels were independently associated with increased risk of having hypertension both in island and in rural residents. The weighted awareness rate (29.9% vs. 17.3%, P<0.001), treatment rate (51.4% vs. 28.5%, P<0.001), and control rate (36.3% vs. 24.0%, P=0.001) of hypertension were all significantly higher in island residents than those in rural residents. In conclusion, our survey shows that the epidemics of hypertension are extremely high in surveyed residents in island and rural areas of Dalian city, while awareness, treatment, and control rats of hypertension in these residents are much lower than the national level. The scenario is even worse in rural residents as compared with island residents of Dalian, China.

1. Introduction

The prevalence of hypertension is increasing constantly in mainland China in line with the population aging process and rapid economic development over recent decades. Hypertension is remarkably related to increased risk of cardiovascular comorbidities and mortality [1]. Based on a national survey of the prevalence of hypertension in China between 2012 and 2015, 23.2% of the Chinese adult population ≥18 years of age suffered from hypertension [2]. There is a significant difference in prevalence of hypertension in various regions of China due to the impact of complex geographical patterns

and economic and cultural diversity. For example, in economically developed regions, the prevalence of hypertension is significantly higher among rural residents than among urban residents (31.3% vs. 29.2%, p=0.001), whereas this disparity in the prevalence of hypertension between urban and rural areas disappeared in the northern region (31.6% vs. 31.2%, p=0.505) [3]. Also, according to the recent data, similar prevalence of hypertension between urban and rural residents in China was reported (23.4% vs. 23.1%, P=0.819) [2]. Therefore, it is of importance to investigate region-related prevalence and related risk factors of hypertension in various regions in order to help formulate and devise local public health strategies and approaches in the prevention and management of hypertension.

In 2012, we conducted an epidemiological survey on prevalence of hypertension on permanent residents living in an island encircled by the Yellow Sea (Zhangzi Island) and residents living on a coast district near the Yellow Sea (Zhuanghe District). Zhangzi Island is one of the islands in the Yellow Sea and 55 km from Zhuanghe District. Most residents on Zhangzi Island live on fishing and fisheries processing. Zhuanghe District lies in the north coast of the Yellow Sea. Most residents in Zhuanghe District live on farming. In present study, we investigated the epidemic features and risk factors of hypertension in the island (Zhangzi Island) and rural (Zhuanghe District) residents; our data might be helpful in the establishment of more effective and targeted prevention and management strategies for residents living in these areas.

2. Methods

2.1. Study Population. A total of 8347 permanent residents aged ≥18 years in Zhangzi Island and Zhuanghe District took part in this survey. Proportion of participants aged <40 years was 10.8% in the island area and 4.7% in the rural area, respectively. Most of young male residents both in island and in rural areas were absent at the time of survey because they lived outside of their hometown for work. Thus, the majority of participants comprised of female and middle-aged or elderly male residents. Eventually, 2652 island residents (716 male and 1936 female) and 5112 rural residents (1750 male and 3362 female) aged ≥40 years were included in this study for the final analysis.

2.2. Questionnaire Survey. "Survey Questionnaire of Cardiovascular Disease Risk Factors" derived from amendatory MONICA study was used in this study [4, 5]. The survey staffs received training on data collection before the survey.

2.3. Definitions. Blood pressure was measured as previously described [6]. Briefly, blood pressure was measured twice by trained examiners following a standardized protocol using aneroid sphygmomanometers. Participants sat with both feet on the floor for at least five minutes before the first measurement. The two blood pressure measurements were taken at least two minutes apart. Hypertension is defined according to "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7) [7]. Patients were divided into 2

subgroups as follows: Group 1, normotensive participants (i.e., no medical history of hypertension and SBP <140 mmHg and DBP <90 mmHg measured at the survey time); Group 2, hypertensive participants (self-reported hypertension with or without antihypertensive medications use or SBP≥140 mmHg and/or DBP≥90 mmHg measured at the survey time). Weight status was defined by body mass index (BMI) according to the lower cutoff values recommended by WHO experts for Asians, i.e., overweight as $BMI \geq 24 \, kg/m^2$ and obesity as $BMI \geq 28 \, kg/m^2$ [8–10]. Participants who were currently smoking cigarettes, bides, or hookah with an average of more than 1 cigarette daily were defined as current daily smokers [11]. Participants who were consuming alcohol within the past 1 year and daily alcohol consumption (alcohol content) ≥25g in men and ≥15g in women were defined as current alcohol drinkers [12]. The highest education level of participants was categorized into 5 levels: illiterate or semiliterate, primary education, secondary education, upper secondary education, and tertiary or higher education.

2.4. Biochemistry Examination. Blood samples were taken from all participants at the time of survey. Laboratory analysis including serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), urea, creatinine, and uric acid (UA) was performed. Hyperuricemia was defined if serum UA >420 μmol/L in men and postmenopausal women and serum UA >360 μmol/L in premenopausal women according to the current recommendations of Chinese experts consensus [13, 14].

2.5. Statistical Analysis. Continuous variables were expressed as mean ± standard deviation (SD) or median (quartiles). Differences on continuous variables between groups were compared using unpaired two-sample Student's t-test after normalization if indicated. Nonnormally distributed variables were compared using Mann-Whitney U test. Categorical variables were compared across groups using a Chi-square test for the overall test and column proportions were compared using z-test. Multivariate binary logistic regression analysis was conducted to determine independent risk factors of hypertension in this cohort. Adjusted odds ratios (ORs) with 95% confidence interval (CI) were calculated. Survey data were weighed based on the Sixth National Population Census of the People's Republic of China in 2010 [15] to calculate weighted prevalence, awareness rate, treatment rate, and control rate of hypertension. A significance level of 0.05 was used. Statistical analysis was performed using IBM SPSS, version 22 for Windows (SPSS).

2.6. Ethical Consideration. Ethical approval was obtained from the Institute Ethical Committee of Zhongshan Hospital of Dalian University. All the participants signed informed consent.

3. Results

3.1. Demographic Data. Table 1 shows the age and sex distribution data of island and rural residents.

TABLE 1: The age and sex distribution in residents living in the island and rural areas.

| Age (years) | Island | | | Rural | | |
	Male N (%)	Female N (%)	Total N (%)	Male N (%)	Female N (%)	Total N (%)
40-49	72 (10.1)	513 (26.5)	585 (22.1)	165 (9.4)	720 (21.4)	885 (17.3)
50-59	128 (17.9)	659 (34.0)	787 (29.7)	368 (21.0)	1051 (31.3)	1419 (27.8)
60-69	304 (42.5)	521 (26.9)	825 (31.1)	707 (39.9)	1065 (60.1)	1772 (34.7)
70-79	166 (23.2)	199 (10.3)	365 (13.8)	394 (22.5)	457 (13.6)	851 (16.6)
≥80	46 (6.4)	44 (2.3)	90 (3.4)	116 (6.6)	69 (2.1)	185 (3.6)
Sum	716	1936	2652	1750	3362	5112

TABLE 2: The systolic and diastolic blood pressures in island and rural residents (mmHg).

| | Island | | | Rural | | |
	Normotensive	Hypertensive	Total	Normotensive	Hypertensive	Total
SBP	116 ± 10	144 ± 18∗	132 ± 21	116 ± 11	144 ± 18∗	133 ± 21
DBP	75 ± 7	92 ± 9∗	84 ± 12	76 ± 6	92 ± 9∗	86 ± 11†

∗ P<0.05 vs. normotensive; † P<0.05 vs. Island. SBP: systolic blood pressure; DBP: diastolic blood pressure.

TABLE 3: Weighted prevalence of hypertension stratified by age and sex [% (95% CI)].

| | Island | | | Rural | | |
	Males	Females	Total	Males	Females	Total
Age (years)						
40-49	59.7 (47.5-71.7)	34.1∗ (30.0-38.4)	47.7 (44.7-50.7)	52.7 (44.8-60.5)	47.6∗ (43.9-51.4)	50.6 (48.2-53.0)
50-59	61.7 (52.7-70.2)	53.6∗ (49.7-57.4)	56.6 (53.5-59.6)	63.0 (57.9-68.0)	64.4 (61.4-67.3)	63.9† (61.6-66.1)
60-69	61.2 (55.5-66.7)	62.8 (58.5-66.9)	61.2 (55.5-66.7)	63.9 (60.3-67.5)	71.4∗ (68.5-74.1)	63.9† (60.3-67.5)
70-79	60.8 (53.0-68.3)	65.8 (58.8-72.4)	63.6 (58.4-68.5)	72.1 (67.4-76.5)	77.7 (73.6-81.4)	75.1† (72.0-78.0)
80-99	78.3 (63.6-89.1)	72.7 (57.2-85.0)	75.6 (65.4-84.0)	69.8 (60.6-78.0)	76.8 (65.1-86.1)	73.6 (67.7-78.9)
Total	61.2 (58.7-63.7)	48.8∗ (46.2-51.5)	55.2 (53.3-57.0)	61.3 (59.5-63.0)	62.6 (60.6-64.5)	61.9† (60.5-63.2)

∗ P<0.05 vs. Males; † P<0.05 vs. Island.

3.2. Weighted Prevalence of Hypertension Stratified by Age and Sex. The systolic blood pressures (SBP) and diastolic blood pressures (DBP) in island and rural residents are shown in Table 2. SBP (144 ± 18 vs. 144 ± 18 mmHg, P>0.05) and DBP (92 ± 9 vs. 92 ± 9 mmHg, P>0.05) were similar between island and rural residents with hypertension.

Totally weighted prevalence of hypertension was significantly higher in rural residents than in island residents (61.9% vs. 55.2%, P<0.001). As shown in Table 3, weighted prevalence of hypertension in island residents was 55.2% (95% CI 53.3-57.0) and was significantly higher in males than in females (61.2% vs. 48.8%, P<0.001). The prevalence of hypertension in rural residents was 61.9% (95% CI 60.5-63.2) and was similar between males and females (61.3% vs. 62.6%, P=0.561).

As expected, the prevalence of hypertension increased with age in both island and rural groups. The hypertension prevalence was significantly lower in island residents than in rural residents at 50-59, 60-69, and 70-79 year age groups, respectively. Hypertension prevalence remained unchanged in various groups of age in male residents, while hypertension prevalence increased continuously after age 50 in female residents living both in island area and in rural area.

3.3. Blood Parameters. As shown in Table 4, serum TC, TG, LDL-C, urea, creatinine, and UA levels were significantly higher and HDL-C was significantly lower in island residents than in rural residents. Serum TC, TG, LDL-C, urea, creatinine, and UA levels were significantly higher in the hypertensive group than in the normotensive group both in island residents and in rural residents. HDL-C was significantly lower in the hypertensive group than in the normotensive group in island residents, while it was similar between groups in rural residents.

3.4. BMI. BMI of island residents was higher in island residents than in rural residents (25.1 ± 3.5 vs. 24.3 ± 3.41, P<0.001). The prevalence of hypertension increased with increasing BMI both in island residents (33.3% in underweight, 44.6% in normal BMI, 55.7% in overweight, and 74.6% in obesity, respectively) and in rural residents (45.7%, 54.2%, 66.4%, and 80.1%, respectively, Table 5).

3.5. Smoking and Alcohol Drinking. In surveyed island residents, proportions of smoking and alcohol drinking were 13.5% (358/2652) and 12.8% (340/2652), respectively. In surveyed rural residents, proportions of smoking and alcohol drinking were 19.3% (998/5112) and 12.7% (651/5112).

TABLE 4: The blood biochemical parameters in island and rural residents.

	Island			Rural		
	Normotensive	Hypertensive	Total	Normotensive	Hypertensive	Total
TC (mmol/L)	5.25 ± 1.01	5.45 ± 1.07∗	5.36 ± 1.05	5.04 ± 0.89	5.15 ± 0.91∗	5.11 ± 0.90†
TG (mmol/L)	1.24 ± 0.71	1.42 ± 0.85∗	1.34 ± 0.80	1.15 ± 0.72	1.29 ± 0.87∗	1.23 ± 0.82†
HDL-C (mmol/L)	1.36 ± 0.32	1.33 ± 0.33∗	1.34 ± 0.32	1.38 ± 0.43	1.37 ± 0.38	1.37 ± 0.40†
LDL-C (mmol/L)	2.40 ± 0.61	2.56 ± 0.70∗	2.49 ± 0.67	2.23 ± 0.57	2.30 ± 0.63∗	2.27 ± 0.61†
Urea (mmol/L)	6.26 ± 1.53	6.57 ± 2.13∗	6.43 ± 1.90	6.04 ± 1.60	6.25 ± 1.78∗	6.17 ± 1.71†
CREA (μmol/L)	66.6 ± 16.1	72.2 ± 52.9∗	69.7 ± 40.9	64.8 ± 12.7	65.9 ± 16.4∗	65.4 ± 15.0†
UA (μmol/L)	317 ± 90	351 ± 92∗	336 ± 92	291 ± 70†	303 ± 75∗	298 ± 73†

∗ P<0.05 vs. Normotensive; †P<0.05 vs. Island. TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CREA: creatinine; UA: uric acid.

TABLE 5: Weighted prevalence of hypertension stratified by BMI in island and rural residents.

	Island		Rural		P value
BMI (kg/m²)	Mean ± SD	25.1±3.5	Mean ± SD	24.3 ± 3.4	<0.001
	No.	Prevalence of HP	No.	Prevalence of HP	<0.001
Underweight	13/43	33.3 (20.0-49.0)	60/145	45.7 (37.8-53.7)	
Normal	464/1032	44.6 (41.7-47.6)	1205/2328	54.2 (52.2-56.2)∗	
Overweight	556/994	55.7 (52.7-58.7)†‡	1245/1908	66.4 (64.2-68.5) ∗†‡	
Obesity	434/581	74.6 (71.0-77.9)†‡§	576/727	80.1 (77.0-83.0) †‡§	
P value		<0.001		<0.001	

∗ P<0.05 vs. Island; † P<0.05 vs. underweight; ‡ P<0.05 vs. Normal; § P<0.05 vs. Overweight. BMI: body mass index; HP: hypertension.

TABLE 6: Awareness rate, treatment rate, and control rate of hypertension in island and rural residents.

	No.	Island (%, 95% CI)	No.	Rural (%, 95% CI)	P value
Awareness rate	805/2649	29.9 (28.2-31.6)	848/5107	17.3 (16.3-18.3)	<0.001
Treatment rate	414/2649	15.4 (14.1-16.7)	246/5107	4.9 (4.4-5.6)	<0.001
Within awareness group	414/805	51.4 (48.0-54.8)	246/848	28.5 (25.6-31.6)	<0.001
Control rate	147/2649	5.6 (4.8-6.5)	57/5107	1.2 (0.9-1.5)	<0.001
Within treatment group	147/414	36.3 (31.8-40.9)	57/247	24.0 (19.0-29.7)	0.001

The weighted prevalence of hypertension was similar between no smoking group and smoking group both in island residents (no smoking 55.1% vs. smoking 55.4%, P=0.963) and in rural residents (62.9% vs. 59.4%, P=0.071).

The weighted prevalence of hypertension was significantly higher in alcohol drinking group than in no alcohol drinking group in island residents (alcohol drinking 64.7% vs. no alcohol drinking 52.9%, P<0.001), while it remained similar between groups in rural residents (61.4% vs. 63.5%, P=0.187).

3.6. *Education Levels.* Proportions of illiterate or semiliterate, primary education, lower secondary education, upper secondary education, and tertiary or higher education were 11.7%, 37.8%, 41.9%, 5.7%, and 2.9% in island residents and were 20.3%, 39.2%, 31.2%, 8.1%, and 1.3% in rural residents, respectively.

The prevalence of hypertension decreased with increase in education levels both in island residents (68.5% vs. 64.7% vs. 46.1% vs. 42.4% vs. 39.5%, P<0.001) and in rural residents (70.3% vs. 57.4% vs. 54.1% vs. 57.9% vs. 44.7%, P<0.001).

Among residents received upper secondary or higher education, the prevalence of hypertension was significantly lower in the island group than in the rural group (41.4% vs. 56.1%, P=0.001), while it was similar between island and rural residents who received lower secondary or lower education (56.7% vs. 59.1%, P=0.062).

3.7. *Awareness Rate, Treatment Rate, and Control Rate of Hypertension.* As shown in Table 6, the weighted awareness rate (29.9% vs. 17.3%, P<0.001), treatment rate (51.4% vs. 28.5%, P<0.001), and control rate (36.3% vs. 24.0%, P=0.001) of hypertension were all significantly higher in island residents than those in rural residents.

As shown in Table 7, calcium channel blockers were most frequently used both in island and in rural residents (42.1% vs. 22.8%, P<0.001). The survey results showed that most hypertensive patients took mono antihypertensive agent both in island and in rural areas. The proportion of combined antihypertensive medication is significantly higher in island residents than in rural residents (32.4% vs. 19.8%, P<0.001). In addition, 47.1% of island residents and 57.1% of rural residents

TABLE 7: Hypertensive mono medication status in island and rural residents.

	Island	Rural	P value
Diuretic	8.7% (36/413)	19.1% (47/246)	<0.001
Beta-blocker	20.5% (85/414)	10.1% (25/247)	<0.001
CCB	42.1% (174/413)	22.8% (56/246)	<0.001
ACEi	14.8% (61/413)	17.9% (44/246)	0.290
ARB	4.3% (18/414)	1.6% (4/246)	0.060
Others	47.1% (195/414)	57.1% (141/247)	0.013

CCB: calcium channel blockers; ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

TABLE 8: Multivariate binary logistic regression analysis of risk factors of hypertension in island residents.

	Wald	P value	OR	95% CI for OR	
				Lower	Upper
Age (years)					
40-49	37.480	<0.001	Reference	-	-
50-59	7.850	0.005	1.333	1.090	1.630
60-69	15.434	<0.001	1.609	1.269	2.040
70-79	12.024	0.001	1.687	1.255	2.268
≥80	22.161	<0.001	3.302	2.008	5.429
Male vs. female	9.077	0.003	1.353	1.111	1.647
BMI					
Underweight/normal	99.762	<0.001	Reference	-	-
Overweight	19.956	<0.001	1.517	1.263	1.821
Obesity	99.388	<0.001	3.299	2.609	4.172
Alcohol drinking	3.302	0.069	1.235	0.984	1.551
Education levels					
Lower secondary or lower vs. upper secondary or higher education	15.667	<0.001	1.805	1.347	2.419
TG (mmol/L)	2.993	0.084	1.104	0.987	1.234
LDL-C (mmol/L)	16.206	<0.001	1.295	1.142	1.469
Urea (mmol/L)	0.406	0.524	1.015	0.969	1.064
UA (umol/L)	25.202	0.001	1.003	1.002	1.004
Constant	103.128	0.001	0.052		

OR: odds ratio; CI: confidence interval; BMI: body mass index; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; UA: uric acid.

took other nonstandard medications, mostly the Chinese herb medicine.

3.8. Independent Risk Factors of Hypertension in Island and Rural Residents. Multivariate binary logistic regression analysis showed that older age, higher BMI, lower education level, and higher LDL-C and UA levels were independently associated with increased risk of having hypertension both in island and in rural residents (Tables 8 and 9). Female sex remained as independent risk factor of hypertension in island residents.

4. Discussion

The major findings of this study included that (1) the prevalence of hypertension adopting JNC 7 guideline was 61.9% in residents of Zhuanghe District (rural area) and it was significantly higher than in residents of Zhangzi Island (island area, 55.2%, $P<0.001$); (2) older age, higher BMI, lower education level, and higher LDL-C and UA

levels were independently associated with increased risk of having hypertension both in island and in rural residents.

4.1. Prevalence and Independent Risk Factors of Hypertension in Surveyed Areas. According to a nationwide survey data from 2012 to 2015, weighted prevalence of hypertension in Chinese adult population aged ≥18 years was 23.2% [2]. Total prevalence of hypertension in Liaoning Province was 28.6% and 30.8% in urban residents and 26.2% in rural residents, respectively [2]. Our survey data showed that the weighted prevalence of hypertension in the island residents aged ≥ 40 years was 61.9% and 55.2% in the rural residents. This prevalence was also higher than nationwide prevalence in community-dwelling adults aged 35-75 years (44.7%) [15]. The awareness rate, treatment rate, and control rate of blood pressure were 46.5%, 41.1%, and 13.8%, respectively, in China. Our survey results showed that the awareness rate, treatment rate, and control rate of hypertension in two surveyed areas are significantly lower than national level. The

TABLE 9: Multivariate binary logistic regression analysis of risk factors of hypertension in rural residents.

	Wald	P value	OR	95% CI for OR	
				Lower	Upper
Age (years)					
40-49	138.232	<0.001	Reference	-	-
50-59	50.701	<0.001	1.821	1.544	2.147
60-69	56.344	<0.001	2.186	1.782	2.681
70-79	77.681	<0.001	3.521	2.662	4.659
≥80	29.730	<0.001	3.437	2.205	5.356
Male vs. female	0.084	0.772	1.026	0.864	1.217
BMI					
Underweight/normal	126.283	<0.001	Reference	-	-
Overweight	67.953	<0.001	1.894	1.627	2.204
Obesity	94.646	<0.001	3.346	2.623	4.268
Alcohol drinking	0.509	0.476	1.075	0.881	1.313
Education levels					
Lower secondary or lower vs. upper secondary or higher education	0.190	0.663	1.055	0.829	1.343
TG (mmol/L)	13.057	<0.001	1.190	1.083	1.308
LDL-C (mmol/L)	7.730	0.005	1.188	1.052	1.340
Urea (mmol/L)	7.042	0.008	1.062	1.016	1.109
UA (umol/L)	0.617	0.432	1.000	0.999	1.001
Constant	38.604	<0.001	0.200		

OR: odds ratio; CI: confidence interval; BMI: body mass index; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; UA; uric acid.

weighted awareness rate in island residents was 29.9%, and 51.4% of them were receiving antihypertensive medications, and among treated patients, control rate was 36.3%. The awareness rate, treatment rate, and control rate in rural residents were 17.3%, 28.5%, and 24.0%, respectively, and were significantly lower than those in island residents. The following points might relate to the alarming hypertension epidemics both in island and in rural areas reported in this study.

The educational level might be responsible for the high prevalence of hypertension. Educational level in the two areas is under average national level; 91.4% population in island and 93.2% population in rural area are mainly junior middle school level or below [16]. Previous survey found that awareness, treatment, and control rates of hypertension were higher in urban residents compared with rural residents, and low education level was associated with lower rates of awareness, treatment, and control rats of hypertension. The slightly better education level in island residents might, therefore, be responsible for slightly better scenario on the higher awareness, medicine adherence, and control rates of hypertension in island residents as compared to the residents in rural area.

Aging is related to higher prevalence in these two surveyed areas, which is in line with the domestic related conclusions [17]. Besides above factors, higher BMI and higher LDL-C and UA levels are found to be the independent risk factors of hypertension in residents of the surveyed residents, in line with previous reports [18–22].

4.2. Treatment and Medication Status. The most common antihypertensive medications included CCB (nifedipine), beta-blocker, and ACEI in island residents and CCB, diuretic, and ACEI in rural residents. It is difficult for most patients to take mono antihypertensive drug to control the hypertension and reach individualized treatment. It is incompatible with the advocated principle of combining of antihypertensive drugs. The antihypertensive effect is not ideal; the island control rate of hypertension is only 36.3%, even 24.0% in the rural area. The slightly better control rate in island hypertensive residents might relate to the factor that the proportion of combined antihypertensive medication was significantly higher in island residents than in rural residents (32.4% vs. 19.8%, P<0.001). While the general unacceptable low hypertension control rate might be related to the widespread use of nonstandard medications, especially the Chinese herb medicine in surveyed hypertensive residents, we found that 47.1% of island residents and 57.1% of rural residents took nonstandard medications to treat their hypertension, mostly the Chinese herb medicine.

5. Conclusion

In conclusion, our survey shows the epidemics of hypertension are extremely high in surveyed residents both in island and in rural areas of Dalian city, while awareness, treatment, and control rates of hypertension in these residents are much lower than the national level. Targeted strategies including health education and standardized hypertension treatment

are warranted to reduce the hypertension burden in these areas.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

A statement should be made that an earlier version of this manuscript has been presented as poster in Journal of Hypertension, which was only an abstract (doi: 10.1097/01.hjh .0000549258.06063.fb).

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Qin Yu designed this study; Baiting Liu and Hainiang Liu helped in revising the manuscript. All authors read and approved the final manuscript; Rongmei Na, Baiting Liu, and Qianxiao Li took part in the whole investigation; Libo Chen, Wencheng Tu, Jiahui Hu analyzed data; Dong Cheng prepared the figures and Yalan Cao and Zhu Li revised the figures; Prof. Weiyi FANG and Prof. Ning ZHU Supervised the experimental process; and Qin YU drafted the manuscript. Baiting Liu and Hainiang Liu contributed equally to this work.

Funding

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Research Article

Hypertension in Jordan: Prevalence, Awareness, Control, and Its Associated Factors

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Objectives. Determine the prevalence, awareness, and control rates of hypertension and their associated factors among Jordanian adults. *Methods*. A multistage sampling technique was used to select a nationally representative sample of adults from the population of Jordan. Trained interviewers collected data using a comprehensive structured questionnaire, measured anthropometric parameters, and collected blood samples. *Results*. This study included a total of 1193 men and 2863 women aged ranged from 18 to 90 year with a mean (SD) of 43.8 (14.2) year. The age-standardized prevalence was 33.8% among men and 29.4% among women. Of those with hypertnsion, 57.7% of men and 62.5% of women were aware of hypertension. Only 30.7% of men and 35.1% of women who were on antihypertensive medications had their blood pressure controlled. From 2009 to 2017, there was nonsignificant decrease in hypertension prevalence of 2.7% among men and 1.1% among women. However, the rate of hypertension awareness increased significantly among men and among women. *Discussion*. Almost one-third of Jordanian adults had hypertension. Interventions that target modifiable risk factors of hypertension, might decrease blood pressure, and even prevent the development of hypertension should be implemnted.

1. Introduction

Hypertension is a modifiable risk factor for cardiovascular and cerebrovascular diseases worldwide [1]. The burden of hypertension is very high because of its high prevalence and its associated mortality and morbidity [2]. One study showed that the prevalence of hypertension is expected to increase by 7.2% from 2013 estimates by 2030 [3]. The complications of hypertension account for 9.4 million deaths worldwide every year and it is estimated that up to 1.58 billion adults will suffer from complications of hypertension by 2025, worldwide [4, 5]. Hypertensive heart disease was the fourth-highest ranked cardiovascular disease cause for DALYs in 2015 globally [6].

About 30% of adults in Arab countries were estimated to have hypertension [7]. In a follow-up study in Jordan comparing hypertension prevalence from 1994 to 2009, the prevalence of hypertension increased from 29.4% to 32.3% [8]. Although screening, early detection, and control of hypertension are associated with decreased risk of stroke, myocardial infarction, and heart failure, preventive and interventional programs are limited and not well structured and organized in Jordan. Moreover, population-based preventive programs are lacking in Jordan. In addition, there is scarcity of recent data on hypertension prevalence, awareness, control, and its risk factors. These data are needed for developing prevention and intervention programs to control and manage hypertension.

This study aimed to determine the prevalence, awareness, and control rates of hypertension and their associated factors among Jordanian adults. Moreover, this study aimed to assess the change in these rates between 2009 and 2017.

2. Methods

2.1. Study Design and Sampling. This survey was conducted among Jordanian adults over a period of four months in the year 2017. The survey methods and procedures are similar to those that had been used in the 2009 survey [8]. A multistage cluster sampling approach with probability proportional to size random selection method was used to ensure adequate coverage of the entire target population. A city/village was selected from each of the 12 governorates of Jordan. The sample of households was chosen in two stages. In the first stage, well-defined geopolitical areas (clusters) were selected from each city/village. At least one cluster was selected from each city/village at random using computer-generated random numbers. The second stage of household selection involved choosing a random sample of households from a list of households in a selected area. The households from each cluster were selected at random using systematic sampling technique. A team of two (a female and a male) visited and invited selected households to report to the health center in that site fasting in a given day after explaining the study for them. Subjects were asked not to take their medications in that day and to bring the medications with them to the health center. Subjects aged ≥18 years were eligible for inclusion in the study. To encourage participation, the team worked on weekends and holidays and provided free transport for those who asked for it. The overall response rate was 78.1%. The total sample participating in the study was 4056 subjects which translates to a margin of error of about 1.3% given a prevalence of 20% and a 95% confidence level.

The study was approved by the Ethical Committee at the National Center for Diabetes, Endocrinology, and Genetics, Amman, Jordan. Informed consent was obtained from each participant. Data were treated with strict confidentiality and used only for scientific purposes.

2.2. Data Collection. Trained interviewers administered a comprehensive structured questionnaire specifically prepared for the purpose of the study. Main data obtained included sociodemographic variables, diabetes and other cardiovascular disease risk factors, morbidity, quality of life and health services, and others. Height, weight, waist and hip circumferences, and blood pressure were carried out in a standard way by trained researchers as explained in the 2009 survey [8].

Three blood samples were drawn from a cannula inserted into the antecubital vein and used for the different laboratory measurements. Tubes containing sodium fluoride potassium oxalate were used for glucose measurement. Samples were centrifuged within 1 hour at the survey site and transferred by separate labeled tubes in ice boxes to the central laboratory of the National Center of Diabetes, Endocrinology, and Genetics in Amman, Jordan. All biochemical measurements were carried out by the same team of laboratory technicians using the same method throughout the study period. Fasting plasma glucose was measured by the glucose oxidase method, using a Cobas Analyzer (Roche).

2.3. Variable Definitions. Hypertension was defined as average measured blood pressure ≥140 mm Hg systolic and/or 90 mm Hg diastolic, or self-reported use of medications for hypertension [9]. Participants were defined as aware of hypertension if they had hypertension and reported being informed about the diagnosis by a physician. Patients were considered controlled if they had hypertension, on antihypertensive medication and had systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg. Body mass Index (BMI) was calculated by dividing the weight in kilogram by the height in meters squared. Participants with BMI of 30 kg/m2 or more were considered obese, while those with BMI values that range between 25 kg/m^2 and <30 kg/m^2 were considered overweight. Metabolic abnormalities including increased waist circumference, raised fasting plasma glucose, high triglycerides level, and low high density lipoprotein (low HDL) were defined according to the International Diabetes Federation (IDF) definition [10].

2.4. Statistical Analysis. Data were entered and analyzed using the Statistical Package for Social Sciences software (SPSS IBM version 20). The raw data file for 2009 was reanalyzed using the same variable definitions to assess the time-trends in hypertension prevalence, awareness, and control. Proportions were used to estimate the prevalence, awareness, and control of hypertension. Overall and age-specific prevalence rates were obtained and reported separately for each gender. To permit comparison between the different surveys and with studies in other countries, we derived age-standardized prevalence rates using the world population as a standard. Ninety-five percent confidence limits were reported standardized rates. Chi-square and crosstabs were used to compare the difference between proportions. Multivariate analysis was conducted using generalized linear mixed models (GLMMs) using a logit link (binary logistic regression) to take into account the clustering of observations. Separate GLMM models were used for assessing the independent effects of individual factors associated with hypertension prevalence, awareness, and control. A p-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Participants' Characteristics. This study included a total of 1193 men and 2863 women. Their aged ranged from 18 to 90 year with a mean (SD) of 43.8 (14.2) year. About 74.6% had increased waist circumference and 42.6% had raised fasting plasma glucose. Table 1 shows the sociodemographic, anthropometric, and clinical characteristics of participants according to gender. Men and women differed significantly in these characteristics.

3.2. Hypertension Prevalence, Awareness and Control. The crude prevalence of hypertension was 41.4% among men and 28.3% among women. The age-standardized prevalence was 33.8% (95% confidence interval (CI): 31.3%-36.3%) among men and 29.4% (95% CI: 28.0%-30.8%) among women. The prevalence of hypertension increased significantly with increasing age among men and women (Figure 1). Of those

TABLE 1: The sociodemographic, anthropometric, and clinical characteristics of participants according to gender.

	Men		Women		Total	P-value
	n	%	n	%	N	
Age (year)						<0.001
<50	648	54.4	1966	68.8	2614	
≥50	543	45.6	890	31.2	1433	
Marital status						<0.001
Single	144	12.1	462	16.1	606	
Married	1049	87.9	2401	83.9	3450	
Region						<0.001
North	390	32.7	922	32.2	1312	
Middle	471	39.5	1295	45.2	1766	
South	332	27.8	646	22.6	978	
Smoking status						<0.001
None smoker	592	49.6	2628	91.8	3220	
Past smoker	206	17.3	46	1.6	252	
Current smoker	395	33.1	189	6.6	584	
Family history of hypertension	665	56.2	1734	61.1	2399	<0.001
Diagnosed with hypertension	336	28.5	614	21.6	950	<0.001
Body mass index (Kg/m^2)						<0.001
Normal	264	22.7	639	22.7	903	
Overweight	479	41.2	822	29.2	1301	
Obesity	419	36.1	1357	48.2	1776	
Increased waist circumference	797	67.3	2198	77.7	2995	<0.001
Diabetes mellitus∗	658	55.2	1069	37.3	1727	<0.001
High triglycerides level	647	54.2	1036	36.2	1683	<0.001
Low HDL	732	61.4	1659	57.9	2391	<0.001

∗Fasting blood sugar >100mg/dl or diagnosed with diabetes or on diabetes medication.

with hypertnsion, 57.7% of men and 62.5% of women were aware of hypertension. Only 30.7% of men and 35.1% of women whoe were on antihypertensive medications had their blood pressure controlled. The rates of hypertesnion awareness and control increased significantly with increasing age among men and women (Figures 2 and 3). Tables 2 and 3 show the prevalence, awareness, and control of hypertension among Jordanian men and women according to participants' characteristics.

3.3. *Change in Hypertension Prevalence, Awareness, and Control between 2009 and 2017.* From 2009 to 2017, there was nonsignificant decrease in hypertension prevalence of 2.7% among men and 1.1% among women. This decrease was consistent in men and women, who had an age-standardized hypertension prevalence of 36.5% (33.9-39.2%) and 30.5% (29.2-31.9%) in 2009, respectively. However, the rate of hypertension awareness increased significantly among men from 39.8% in 2009 to 57.7% in 2017 and among women from 51.8% in 2009 to 62.5% in 2017. Similarly, the rate of hypertension control increased from 17.4% to 30.7% among men and from 18.6% to 30.7% among women between 2009 and 2017.

3.4. *Factors Associated with Hypertension Prevalence, Awareness, and Control.* In the multivariate analysis (Table 4), age ≥50 year, increased waist circumference, family history

of hypertension, elevated triglycerides level, and increased plasma glucose were significantly associated with increased odds of hypertension among men and women. Married men and women and those with low HDL had higher odds of hypertension. On the other hand, people aged ≥50 years, married people, those with a family history of hypertension, and current smokers were more likely to be aware of hypertension. Of all variables, only age was associated with hypertension control among men. Men aged ≥50 year were twice more likely to have controlled hypertension compared to those aged <50 years. Among women, those aged 50 year and married women were more likely to have controlled hypertension.

4. Discussion

This study showed that almost one-third of Jordanian adults had hypertension. The age-standardized prevalence of hypertension was 33.8% among men and 29.4% among women. The prevalence of hypertension varies widely across the Arab countries. A systematic review of 13 studies from 10 Arab countries reported an overall estimated prevalence of hypertension of 29.5% [7]. Another systematic review reported an overall worldwide prevalence of 26% in the adult population [11]. The differences in the prevalence rates between countries might be explained differences among studied populations,

Table 2: The prevalence, awareness, and control of hypertension among men in Jordan according to participants' characteristics.

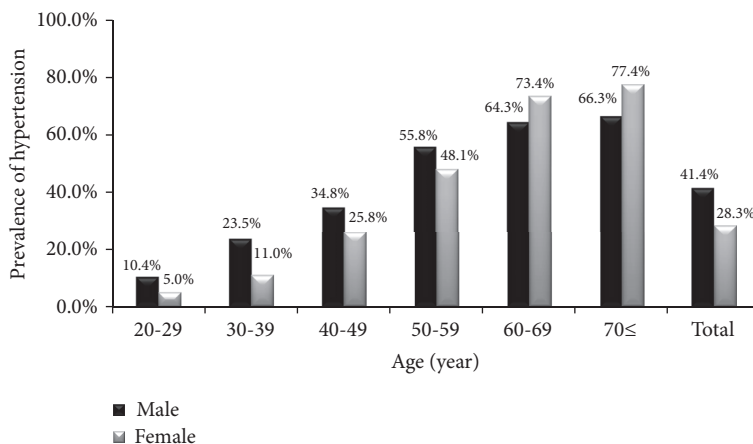|	Hypertension			Awareness of hypertension			Control of hypertension		
	n	%	p-value	n	%	p-value	n	%	p-value
Age (year)			<0.001			<0.001			.001
<50	167	25.9		74	44.3		35	21.0	
≥50	325	60.1		210	64.6		116	35.7	
Marital status			<0.001			.001			.053
Single	14	9.9		2	14.3		1	7.1	
Married	478	45.7		282	59.0		150	31.4	
Smoking status			<0.001			<0.001			.011
None smoker	258	43.8		124	48.1		65	25.2	
Past smoker	103	50.0		79	76.7		42	40.8	
Current smoker	131	33.3		81	61.8		44	33.6	
Region			<0.001			.340			.864
North	167	43.0		104	62.3		51	30.5	
Middle	178	37.9		99	55.6		57	32.0	
South	147	44.5		81	55.1		43	29.3	
Family history of hypertension			.058						.217
Yes	292	44.0		188	64.4		96	32.9	
No	199	38.5		96	48.2		55	27.6	
Body mass index (Kg/m^2)			<0.001			.330			.874
Normal	59	22.3		34	57.6		20	33.9	
Overweight	198	41.3		109	55.1		61	30.8	
Obesity	217	51.8		135	62.2		66	30.4	
Wasit circumference			<0.001			.076			.394
Normal	93	24.0		46	49.5		25	26.9	
Increased	398	49.9		237	59.5		125	31.4	
Diabetes			<0.001			.016			
No	142	26.7		70	49.3				.602
Yes	350	53.4		214	61.1		46	32.4	
Triglycerides level			<0.001			.602			
Normal	178	32.8		100	56.2		55	30.9	
High	314	48.6		184	58.6		96	30.6	
HDL			.014			.100			.978
Normal	169	37.0		89	52.7		52	30.8	
Low	323	44.2		195	60.4		99	30.7	

Figure 1: The prevalence of hypertension among Jordanian adults according to age.

TABLE 3: The prevalence, awareness, and control of hypertension among women in Jordan according to participants' characteristics.

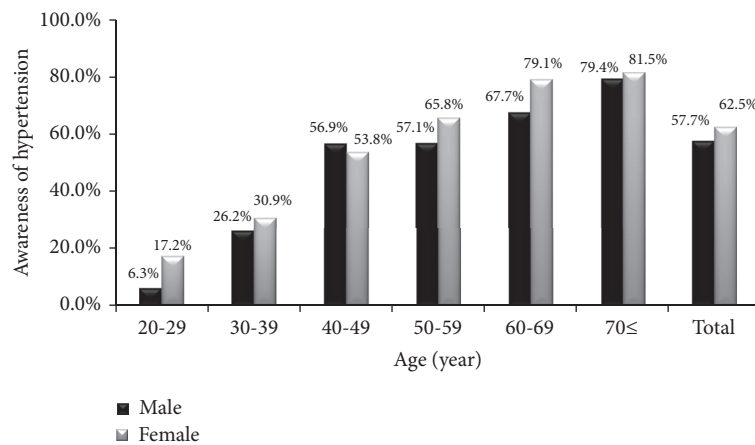|	Hypertension			Awareness of hypertension			Control of hypertension		
	n	%	p-value	n	%	p-value	n	%	p-value
Age (year)			<0.001			<0.001			.004
<50	292	15.0		131	44.9		84	28.8	
≥50	510	58.0		370	72.5		198	38.8	
Marital status						.000			.001
Single	53	11.6		11	20.8		7	13.2	
Married	750	31.5		491	65.5		275	36.7	
Smoking status			.160			.001			.003
None smoker	725	27.9		438	60.4		241	33.2	
Past smoker	17	37.0		14	82.4		8	47.1	
Current smoker	61	32.6		50	82.0		33	54.1	
Region			0.431			.794			.532
North	256	28.0		156	60.9		87	34.0	
Middle	352	27.2		224	63.6		120	34.1	
South	195	31.1		122	62.6		75	38.5	
Family history of hypertension			<0.001			<0.001			.005
Yes	567	33.0		387	68.3		217	38.3	
No	234	21.4		115	49.1		65	27.8	
Body mass index (Kg/m^2)			<0.001			.160			.335
Normal	48	7.5		24	50.0		12	25.0	
Overweight	163	19.9		106	65.0		58	35.6	
Obesity	578	42.7		363	62.8		205	35.5	
Wasit circumference			<0.001			.005			.058
Normal	35	5.6		14	40.0		7	20.0	
Increased	763	34.7		484	63.4		272	35.6	
Triglycerides level			<0.001			.000			.940
Normal	365	20.3		204	55.9		118	32.3	
High	438	42.4		298	68.0		164	37.4	
HDL			<0.001			.079			.393
Normal	240	20.3		139	57.9		79	32.9	
Low	563	34.1		363	64.5		203	36.1	
Diabetes			<0.001			<0.001			
No	302	17.0		147	48.7				.032
Yes	501	47.1		355	70.9		92	30.5	

FIGURE 2: The rate of hypertension awareness among Jordanian adults according to age.

TABLE 4: The multivariate analysis of factors associated hypertension prevalence, awareness, and control.

| | *Men* | | *Women* | |
	OR (95% Confidence interval)	P-value	OR (95% Confidence interval)	P-value
Prevalence of Hypertension				
Age (≥50 vs. <50)	3.3 (2.5, 4.4)	<0.001	5.0 (4.1, 62)	<0.001
Increased waist circumference	2.0 (1.5, 2.8)	<0.001	3.7 (2.5, 5.5)	<0.001
Marital status (married vs. single)	2.2 (1.2, 4.1)	0.015		
Family history of hypertension	1.5 (1.1, 2.0)	0.004	1.9 (1.6, 2.4)	<0.001
Elevated triglycerides level	1.6 (1.2, 2.1)	0.001	1.4 (1.2, 1.8)	0.001
Diabetes	1.7 (1.3, 2.2)	<0.001	1.4 (1.1,1.7)	<0.001
Low HDL	1.4 (1.1, 1.7)	0.004		
Awareness of hypertension				
Family history of hypertension	2.8 (1.8, 4.4)	<0.001	3.2 (2.2, 4.6)	<0.001
Age (≥50 vs. <50)	2.5 (1.6, 3.9)	<0.001	3.4 (2.5, 4.8)	<0.001
Marital status (married vs. single)	5.6 (1.2, 26.7)	0.032	6.3 (3.0,13.0)	<0.001
Smoking				
None smoker	1		1	
Past smoker	3.4 (2.0, 6.2)	<0.001	3.2 (0.8,13.6)	0.114
Current smoker	1.8 (1.1, 3.0)	0.009	2.9 (1.4, 6.1)	0.004
Control of hypertension				
Age (≥50 vs. <50)	1.8 (1.5, 2.3)	<0.001	3.0 (2.2, 4.1)	<0.001
Marital status (married vs. single)			5.9 (2.9, 11.9)	<0.001
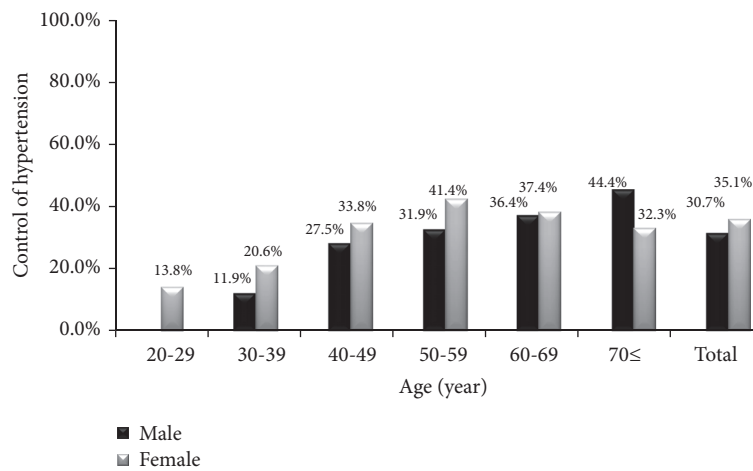
FIGURE 3: The rate of hypertension control among Jordanian adults according to age.

sampling methods, study settings, and timeframes of the studies. The high rate of obesity and physical inactivity and high salt and fat intake in Jordan might explain the high prevalence of hypertension in Jordan as well as other Arab countries.

Consistent with the findings of many studies in the world [12, 13], including studies in Arab countries [8, 14], the rate of hypertension was found to increase by age in both genders. In our study, the prevalence was significantly higher among men than that in women. This finding is consistent with the findings of some studies in Arab countries [14–16]. However, other studies found that hypertension is more common in women [17–19]. No significant gender difference in the rate of hypertension was reported in other studies [20, 21].

Our study showed that 57.7% of men and 62.5% of women were aware of hypertension. The systematic review of studies in Arab countries showed that the awareness of hypertension varied from 18% to 79.8% with an overall rate of 46% [7]. A systematic review of studies worldwide showed that the awareness rates ranges from 25 to 75% [11]. Almost half to two-thirds of patients with hypertension in developed countries were aware of their diagnosis [11]. The rate of hypertension awareness in Jordan increased significantly from 39.8% in 2009 to 57.7% in 2017 among men and from 51.8% in 2009 to 62.5% in 2017 among women. The increased awareness from 2009 to 2017 might be explained by the better access to healthcare services in Jordan in the last 10 years.

Almost one-third (30.7% of men and 35.1% of women) of Jordanian adults on antihypertensive medications had controlled hypertension. The rate of hypertension control in Arab countries varied from 8% to 44% [15–20]. The low control rate was also seen in USA and European countries [12]. The poor hypertension control in Jordan might be explained by inadequate management of hypertension, not using evidence based practices in management of hypertension, and poor adherence to medication. On the other hand, the rate of hypertension control increased from 17.4% to 30.7% among men and from 18.6% to 30.7% among women between 2009 and 2017. The improved level of peoples' awareness and improved access to health services over the last few years might explain the increase in the rate of hypertension control.

The multivariate analysis showed that patients aged ≥50 years were more likely to have hypertension, to be of aware of the diseases and to have better control compared to younger patients. The higher rate of hypertension awareness and control among older patients might be explained by that old patients have more frequent visits to health facilities because of other comorbidities and have a higher chance to be informed of their blood pressure and to be prescribed medications to control hypertension. Family history of hypertension was also associated with higher odds of hypertension and awareness of hypertension. Patients with family history of hypertension might learn from their families' experiences and be more likely to attend the health center to check their blood pressure. Increased waist circumference, diabetes, and low HDL were all associated significantly with hypertension. These variables are well-known risk factors for cardiovascular diseases and had been show to cluster in a form of metabolic syndrome.

In conclusion, almost one-third of Jordanian adults had hypertension. Of those with hypertension, more than half of men and about two-thirds of women were aware of hypertension. Only one-third of those who were on antihypertensive medications had controlled blood pressure indicating gaps in the management of hypertension in this country. Interventions that target modifiable risk factors of hypertension, might decrease blood pressure, and even prevent the development of hypertension should be implemnted. Evidence-based prevention and management recommendations and guidelines including lifestyle modifications need to be adopted in Jordan.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

Authors have no conflicts of interest to declare.

Acknowledgments

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Research Article
Arterial Hemodynamics in Prehypertensives

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Compared to age-matched normotensive adults, those with essential hypertension have been shown to have distinct arterial hemodynamic abnormalities consisting of increased peripheral resistance, pulse wave velocity, and wave reflection magnitude as well as decreased wave reflection time and aortic compliance. These abnormalities are further exacerbated by beta-adrenergic blockade. To see if there are similar hemodynamic abnormalities that antedate the onset of fixed hypertension, we compared age-matched normotensives with prehypertensives selected from patients undergoing diagnostic cardiac catheterization. Ascending aortic pressure and flow were measured with a micromanometer and flow velocity sensor in the baseline state and after beta-adrenergic blockade. In the baseline state the prehypertensive compared to the normotensive group had elevated blood pressure, resistance, left ventricular end-diastolic pressure (LVEDP), and wave reflections. Beta-adrenergic blockade increased resistance, LVEDP, and wave reflections in both groups. Some of these findings are the same as those we previously reported in young persons with established, essential hypertension. The differences in LVEDP and wave reflections, both in the baseline state and after beta-blockade, were still present in subgroups with no differences in blood pressure. Hence, the elevated wave reflections in prehypertensives do not appear to be directly related to the level of blood pressure. These results support the notion that the elevated blood pressure in hypertension may represent a later manifestation of an already abnormal vascular system rather than the vascular abnormalities resulting from hypertension. Consequently, even before blood pressure becomes elevated, early diagnosis and treatment of the vascular abnormalities in prehypertensives may be warranted.

1. Introduction

Both invasive and noninvasive studies have documented distinct hemodynamic abnormalities in people with essential hypertension compared with age-matched normotensives [1–6]. Although there are some minor differences in findings, the consensus is that, compared to normal, peripheral resistance (R), characteristic impedance (Z_c), pulse wave velocity (PWV), and wave reflection magnitude are increased and aortic compliance and wave reflection time are decreased. Acute administration of nonvasodilating adrenergic blockers and angiotensin converting enzyme inhibitors lowers blood pressure but does not normalize all the vascular properties. In contrast, administering a nonspecific smooth muscle dilator, nitroprusside, or a calcium-channel blocker lowered the

blood pressure to the same extent but completely normalized the vascular abnormalities [1]. Therefore, these observations suggest that, in the early stage of essential hypertension, some hemodynamic abnormalities cannot be attributed, per se, to the elevated blood pressure but rather are a manifestation of reversible dysfunction in the muscular arteries modulated by smooth muscle.

Given the above observations, it is reasonable to ask whether the hemodynamic abnormalities are a consequence of or antedate the increased blood pressure. Answering this question is difficult once hypertension becomes manifest because acutely lowering the blood pressure may not be sufficient to reverse some of the longstanding neural or humoral vascular effects. If there is clear evidence of vascular abnormalities before the blood pressure becomes chronically

elevated, this would help clarify this important "chicken vs. egg" issue. If chronically elevated blood pressure eventually causes vascular and target organ abnormalities, then treating the blood pressure in hopes of preventing, or even reversing, potential further damage makes sense. If, on the other hand, vascular changes antedate the onset of blood pressure increases, it might make sense to diagnose and perhaps treat the vascular abnormalities as early as possible so as to either prevent or ameliorate the later manifestations of increased blood pressure. In fact, treating the blood pressure at a later stage might be too late to reverse some of the early vascular abnormalities.

Comparing vascular function in completely normal persons with that in prehypertensives who have a strong family history and likelihood of later developing fixed hypertension but who are not yet hypertensive is one way to directly address the "chicken or egg" issue. This is the rationale for the present study. We obtained acending aortic high-fidelity micromanometric pressure and flow data during cardiac catheterization in a group of prehypertensives and a group of age-matched normotensives. We compared R, aortic impedance, pulse wave reflection magnitude, wave reflection travel time, and compliance during baseline conditions and after acute beta-adrenergic blockade with intravenous propranolol. The results demonstrate that, compared to normotensives, prehypertensives have mildly but statistically significantly higher blood pressure, LVEDP, wave reflections, and R—abnormalities very similar to those previously found in established essential hypertension. More importantly, the elevated wave reflections and LVEDP are present even in subgroups with matched blood pressure. Hence, the presence of early vascular abnormalities in prehypertension together with the increasing recognition of its deleterious effects and predilection for progressing to hypertension [7, 8] suggests that we reconsider our approach.

2. Materials and Methods

2.1. Patient Selection. The study population was selected from ethnic Chinese who were undergoing diagnostic cardiac catheterization for chest pain syndrome, evaluation of a systolic murmur, or electrophysiological evaluation. Exclusion criteria included the following: (1) evidence of congenital, coronary, or valvular heart disease; (2) age under 18; (3) pregnancy; (4) taking of medications that could affect blood pressure such as oral contraceptives, pain relievers, and antidepressants; (5) diabetes mellitus (based on fasting blood glucose level); (6) abnormal renal function based on renal arteriograms and abnormal levels of serum electrolytes, creatinine, blood urea nitrogen, and 24-hour creatinine clearance; (7) abnormal levels of cortisol, 17-ketosteroids, 17-hydroxycorticosterone, aldosterone, plasma renin activity, thyroid stimulating hormone, triiodothyronine, and free thyroxine. Based on multiple outpatient and in-hospital precatheterization standard syphgmomanometric blood pressure measurements, the patients were classified into the normotensive (N) or prehypertensive (P) main groups according to the 2003 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure report (JNC 7) [9]. Those in the N main group had no instances of elevated blood pressure and no family history of hypertension. Those in the P main group had at least one instance of abnormally high blood pressure that normalized during hospitalization and the majority had unequivocal family histories of hypertension. None had a history of being treated with antihypertensive medications. All patients gave informed consent for the investigative portion of the study which was performed with the approval of and according to the guidelines of the hospital's human investigation committee.

2.2. Data Acquisition. All studies were performed as previously reported [10]. Briefly, patients were premedicated with 5 mg intramuscular chlorpheniramine maleate. After completion of the diagnostic portion of the catheterization, baseline high-fidelity left ventricular pressure, ascending aortic pressure, and flow velocity were first recorded for offline analysis. To assess the role of nonspecific beta-adrenergic blockade and to minimize beta-adrenergically mediated peripheral vasodilation, we intravenously administered propranolol at a rate of 1 mg/min until a dose of 0.15 mg/kg had been delivered. Hemodynamic measurements were repeated immediately on completion of beta-blockade.

2.3. Calculations and Data Analysis. Calculations and data analysis methods are identical to those previously reported [10]. Briefly, the pressure and flow signals were digitized at a rate of 250 Hz and resolved into their Fourier harmonics from which input impedance modulus and phase angle, R, Z_c, the frequency of the first zero crossing of the impedance phase angle (f_0), total external power, oscillatory power, and the ratio of oscillatory to total power were calculated. We calculated the amplitudes of the forward (P_f) and backward (P_b) waves and used the ratio P_b/P_f as an index of wave reflection. Finally, since our previous studies have revealed concordant changes in compliance calculated at the different pressure values, for this study we restricted attention to the compliance at peak systolic pressure.

2.4. Statistical Analysis. For statistical analysis we used a two-way, mixed-factorial repeated measures analysis of variance (ANOVA) with the *between-subjects* factors being normotensive and prehypertensive and *within-subjects* factors being baseline and after propranolol. Statistical significance was considered to be $P<0.05$. We first examined all parameters in each main group for each condition for equality of variances using Levene's test and applied an appropriate correction for subsequent analysis only if the variances were not equal. Next, only those variables that exhibited significant *between-subjects* effects were subjected to further analysis, i.e., to discern if there were baseline differences, an effect of beta-blockade, and whether that effect differed between the main groups. Any parameter that had both significant *between-* and *within-subjects* effects was examined for an interaction effect. If no significant interaction was present, the simple main effects were compared. If there was a significant interaction,

Table 1: Clinical characteristics (mean ± SD) of the entire study population comprised of the N and P main groups and subgroups.

Parameter	Main groups		Subgroups	
	Normotensives (N)	Prehypertensives (P)	Normotensives (N)	Prehypertensives (P)
Number	14	12	7	7
Male/female	10/4	11/1	5/2	7/0
Positive family history	0	9	0	4
Age (yrs)	32.4 ± 7.5	33.4 ± 5.7	34.0±6.5	33.0±7.3
Body length (cm)	167.3± 9.0	167.8 ± 7.6	166.4±9.9	171.4±4.6
Body weight (kg)	66.9 ± 12.5	72.3 ± 5.7	68.3±13.3	73.4±6.9
Aortic CSA (cm^2)	6.02 ± 1.36	7.13 ± 1.89	6.73±1.12	6.83±2.26

P=NS for all N vs. P parameters.

further analysis was performed to uncover any specific significantly different pairwise comparisons.

3. Results

3.1. Results

3.1.1. Clinical Characteristics: Table 1.
The left section of Table 1 shows the clinical characteristics of the N and P main groups. Nine of the 12 patients in the P group had an unequivocal family history of hypertension. Although the proportion of women in the N group was greater than in the P group, there was no statistically significant difference in age, body length, body weight, or aortic cross-sectional area. The corresponding data for the subgroups are shown in the right section of the table and similarly indicate no statistically significant differences between the subgroups.

3.1.2. Cardiovascular Parameters: Table 2.
The left section in Table 2 shows the pertinent cardiovascular parameters for the main groups in the baseline state and after propranolol. The right section shows the results for the subgroups. The baseline hemodynamic data for the N group have been reported previously [10] but are included here for completeness and ease of comparison. The data after propranolol have not been previously reported. Even restricting attention to only those parameters with significant *between-subjects* effects, there are so many pairwise comparison results with differing levels of statistical significance that the results of the statistical analysis are presented in a separate table for clarity.

3.1.3. Statistical Analysis Results: Table 3.
The relevant results of the statistical analysis are shown in Table 3. Only the results for those parameters with statistically significant *between-subjects* effects are included. In the baseline state, compared to N, the P main group had significantly higher systolic and diastolic aortic blood pressure, R, LVEDP, P_b, and P_b/P_f. In both groups, as expected, beta-blockade significantly decreased heart rate and increased LVEDP and R. Beta-blockade also increased both P_b and P_b/P_f in both groups with the differences between groups remaining significant. A small but statistically significant increase in systolic blood pressure (SBP) occurred only in the P group after beta-blockade.

Because the P main group had slightly, but statistically significantly, higher blood pressures than the N main group, some or all of the above results might be attributable to the pressure differences. To directly examine this possibility within each of the N and P main groups we selected subgroups whose blood pressure was closer. Specifically, we separately analyzed those in the N group with peak SBP ≥115 and those in the P group with SBP ≤ 130. The results of the subgroups analyses are shown in the right sections of Tables 1–3. As expected, there were no differences in baseline blood pressure between the subgroups. Despite this, LVEDP, P_b, and P_b/P_f are significantly higher and HR is significantly lower in the P than in the N subgroup, both before and after beta-blockade.

Figure 1 shows plots of ascending aortic pressure and its forward and backward components for one beat during baseline and after propranolol for a patient from the N subgroup and one from the P subgroup. Although they are small, there are clear differences between P_b in the N and P patients. For the N patient the small P_b that rises throughout systole to a broad dome under both conditions adds to the dome-shaped P_f to produce a similar dome-shaped pressure wave that peaks in late systole. In contrast, for the P patient, the decrease in P_f beginning early in and continuing through the rest of systole is offset by a larger P_b that rises to a distinct peak resulting in a composite wave with a prominent late systolic peak, especially after propranolol.

4. Discussion

The novelty of this study is the detailed hemodynamic characterization of a group of young prehypertensives who have nearly normal levels of blood pressure and consequently have never been treated, either acutely or chronically, with any antihypertensive medications. There are three major findings which provide some new insights into prehypertension. Compared to pressure- and age-matched normotensives, prehypertensives have (1) elevated wave reflections, (2) no difference in wave reflection travel time, and (3) elevated LVEDP. This strongly suggests that these abnormalities are not directly attributable to the level of blood pressure. To our
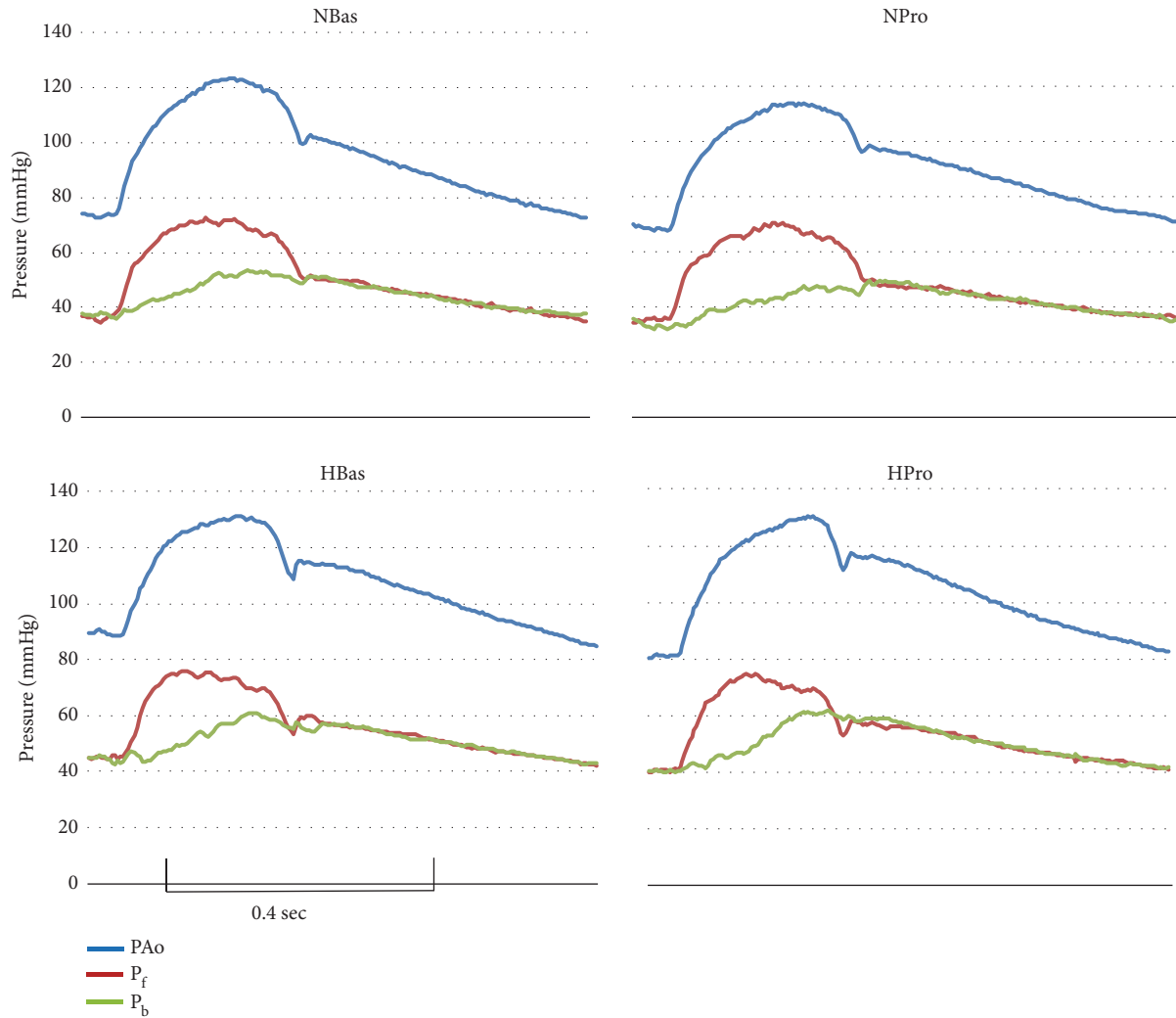
FIGURE 1: Representative plots of aortic pressure and its forward and backward components from one beat during baseline (Bas) and after propranolol (Pro) of one patient from the N subgroup and one from the P subgroup. The corresponding P_f (mmHg), P_b (mmHg), and P_b/P_f values for each beat are as follows: NBas: 37.9, 17.4, and 0.46; PBas: 34.0, 18.3, and 0.54; NPro: 36.3, 17.6, and 0.48; PPro: 34.7, 21.8, and 0.63.

knowledge, this is the first direct evidence of the dissociation between wave reflections and blood pressure. Several previous studies provide corroborating indirect evidence of this dissociation. In more than 40 similarly aged ethnic Chinese with blood pressure much higher than in our P main group, the range of baseline P_b/P_f was in the same range as we found [1]. When either nitroprusside or a calcium-channel antagonist was administered to hypertensives, despite the blood pressure decreasing significantly—but still remaining higher than normal—the wave reflection index completely normalized. When normotensives and hypertensives performed handgrip exercise, despite the systolic blood pressure increasing by about 20 mm Hg in both groups, there was no effect on the wave reflection index [11]. Another study reported dissociation between exercise-induced blood pressure changes and wave reflections in treated hypertensives [12].

There is increasing evidence in muscular arteries of the important role of smooth muscle in modulating wave reflections. The fact that elevated wave reflections and central blood pressure augmentation can be normalized with dilating as compared with nondilating antihypertensive drugs [1, 13, 14] demonstrates that the enhanced wave reflections are not due to fixed structural entities. The increase in wave reflections after beta-blockade observed in both the N and P groups of this and a previous study [15] is consistent with previous results implicating modulation by the autonomic nervous system [3, 16]. There is also increasing evidence for a role of the endothelium in the elevation of wave reflections. Limited nitric oxide availability was reported in hypertensives [17]. Two recent studies reported an association between specific eNOS gene polymorphisms and several abnormal indices of vascular function in age-matched normotensives and prehypertensives [18, 19] thereby providing a mechanistic basis for the vascular changes. A similar level of endothelial damage was observed in young prehypertensives as compared to age-matched hypertensives [20]. As has been emphasized, however, endothelial dysfunction alone

TABLE 2: Baseline (Bas) and after-propranolol (Pro) hemodynamic parameters (mean ± SD) in the main groups and the subgroups.

Parameter	Main groups				Subgroups			
	Normotensives (N) (n=14)		Prehypertensives (P) (n=12)		Normotensives (N) (n=7)		Prehypertensives (P) (n=7)	
	Bas	Pro	Bas	Pro	Bas	Pro	Bas	Pro
HR	83.5±13.5	74.3±9.7	76.1±6.1	67.3±4.0	89.6±13.7	76.6±10.4	74.2±5.2	66.6±4.1
SV	74.9±15.0	75.8±17.6	79.9±11.9	75.6±16.3	73.3±6.9	75.8±8.5	80.1±9.7	73.6±12.5
LVEDP	10.2±4.1	13.8±3.4	17.7±4.2	20.3±4.8	10.6±4.4	13.9±3.6	18.7±4.7	19.6±5.8
SBP	111.8±11.3	113.5±10.6	129.1±6.7	133.2±10.0	120.6±5.5	119.9±7.3	125.4±5.7	128.6±9.5
DBP	73.5±9.9	74.0±9.7	84.5±5.8	86.1±7.3	80.0±4.5	78.8±7.1	81.4±5.0	83.0±7.5
R	1239±224	1402±296	1435±266	1788±434	1257±219	1410±267	1414±177	1763±338
Z_c	75.5±21.5	69.0±20.5	70.8±17.3	72.0±18.2	72.7±14.4	66.1±13.9	75.2±16.1	78.9±16.3
W_t	1497±347	1383±441	1687±346	1412±340	1693±234	1471±195	1596±264	1314±241
W_o/W_t	0.15±0.03	0.14±0.03	0.14±0.02	0.13±0.02	0.15±0.02	0.14±0.03	0.14±0.02	0.13±0.03
P_f	31.9±3.8	30.5±3.7	33.1±4.9	32.1±4.2	33.4±3.8	31.4±4.6	33.4±4.4	32.5±4.8
P_b	13.8±2.5	15.6±2.5	18.5±2.4	20.8±3.4	14.4±2.8	15.8±3.0	18.2±2.3	20.1±3.7
P_b/P_f	0.43±0.07	0.51±0.06	0.56±0.06	0.65±0.08	0.43±0.08	0.51±0.08	0.55±0.06	0.63±0.10
f_0	3.1±0.6	3.3±0.6	3.6±0.7	3.8±0.8	3.5±0.5	3.5±0.3	3.5±0.6	3.6±0.9
C_s	1.8±0.8	1.7±0.8	1.4±0.4	1.2±0.4	1.6±0.5	1.5±0.4	1.4±0.4	1.3±0.4

Abbreviations: HR = heart rate (bpm); SV = stroke volume (ml); LVEDP = left ventricular end-diastolic pressure (mmHg); SBP/DBP = peak systolic/diastolic aortic blood pressure (mmHg); R = peripheral resistance (dyne-sec/cm^5); W_t = total external power (milliwatts); W_o = oscillatory external power (milliwatts); Z_c = characteristic impedance (dyne-sec/cm^5); P_f = magnitude of forward aortic pressure component (mmHg); P_b = magnitude of backward aortic pressure component (mmHg); f_0 = first zero-crossing of aortic impedance modulus (Hz); C_s = aortic compliance at peak systolic blood pressure (ml/mmHg).

TABLE 3: Statistical results of only those parameters in Table 2 with statistically significant between-subjects effects for the main groups and subgroups.[*]

Parameter	Main groups				Subgroups			
	NBas-PBas	NBas-NPro	PBas-PPro	NPro-PPro	NBas-PBas	NBas-NPro	PBas-PPro	NPro-PPro
HR		.001	<.001	.03	.017	<.001	.001	.04
LVEDP	<.001	.01	.03	.001	.01	.04		.05
SBP	<.001			.01	<.001			
DBP	.002			.002				
R	.05	.01	<.001	.01				
P_b	<.001	.002	.001	<.001	.02	.002	.04	.03
P_b/P_f	<.001	<.001	.003	<.001	.01	.001	.03	.02

[*]The P values listed are for simple main effects except that R for the entire population and HR for the subgroups had significant *within-* and *between-subjects* interaction effects. The P values from pairwise comparisons for those two sets of data are shown.

is not necessarily associated with hypertension [17]. For endothelial dysfunction to be deleterious its manifestations must negatively impact other regions of the cardiovascular system—such as via wave reflections.

In the arterial system reflections arise from aortic tapering, branch points, and adjacent regions of differing stiffness. The specific site(s) of reflection are, however, difficult to pinpoint. There appears to be a major reflection near the renal arteries as well as near the iliac bifurcation [21]. In contrast, a modeling study demonstrated nearly equal reflections from the proximal and distal aortic regions [22]. Regardless of site of origin, the reflections merge to produce the resultant central aortic reflected pressure wave whose effects depend critically on morphology, magnitude, and timing [4, 12, 14, 22–24]. If the reflection time is sufficiently long so that the bulk of the backward wave arrives in the ascending aorta during diastole the reflections would have little impact on cardiac loading. Conversely, if reflection time is sufficiently

short so that the bulk of the reflected wave arrives during systole, peak and pulse pressure will be increased which will be detrimental to the heart and other organs.

In the present study, unlike in fixed hypertensives [1], we found no significant difference between the groups in f_0. This is not altogether surprising since the major determinants of f_0 are arterial pulse wave velocity (PWV) and/or the effective wave reflecting site [25]. Even though we did not directly measure PWV, the normal value of f_0 and the mildly elevated blood pressure in the P main group strongly suggests that PWV was not substantially elevated in the prehypertensives. If either PWV were sufficiently increased or the reflecting site were sufficiently proximal in the presence of elevated wave reflections, we would have observed a more marked elevation of central systolic blood pressure.

The small but significant increase above normal in LVEDP in both our P main group and subgroups is evidence for an early, subtle alteration in cardiac function. Since

elevated blood pressure with its attendant increased stresses on the heart does not appear to be responsible, it is reasonable to ask how abnormally high wave reflection but normal wave reflection time can be deleterious. It is plausible that some daily activities—such as those involving isometric exercise or even mental stress—transiently increase blood pressure which in turn increases PWV and thereby sufficiently shortens wave reflection time to affect systolic function. Over a prolonged period, without needing to invoke chronic mechanisms such as fixed vascular damage or anatomic abnormalities, this transient loading could be deleterious. There is some indirect evidence supporting this contention. Handgrip exercise in both normotensives and hypertensives shortened wave reflection time without affecting P_b/P_f [11]. PWV during handgrip exercise, independent of wave reflection magnitude, was found to be the strongest predictor of LV mass index in treated hypertensives [12]. In young men with low, normal, and high normal blood pressure, a mental stress challenge induced significantly different increases in both blood pressure and catecholamines that were directly related to the baseline pressure levels [16]. In contrast, wave reflection magnitude, but neither PWV nor wave reflection time, was found to be the strongest predictor of LV mass regression during a year of treatment in hypertensives [24]. The lack of effect of PWV could be because the already elevated PWV blunted any additional effect. Another study in a general population of men and women found that aortic compliance, peripheral resistance, and reflected wave magnitude were independent predictors of increased LV mass [26]. That study, however, did not examine the effect of wave reflection time. In addition to wave reflections, there is other evidence of abnormal ventricular diastolic function as manifested in prolonged isovolumic relaxation time and slower filling in prehypertensives compared to normotensives [27].

These short-term, reversible effects of wave reflections will also be affected by chronic effects. One example is aging which is well known to increase stiffness of the large arteries. The resultant increase in PWV shortens reflection time and thereby increases central arterial systolic and pulse pressure [28, 29]. The former puts an additional load on the heart and the latter transmits pressure waves deeper into target organs. Moreover, the increased arterial pressure distends the large arteries causing an even greater increase in stiffness—resulting in a deleterious vicious cycle. In prehypertensives with already elevated wave reflections these deleterious effects could not only begin earlier but also be more pronounced with aging than in normotensives. Indeed, some long-term effects of elevated wave reflections have been reported [4, 30]. In the latter study, an elevated P_b—independent of heart rate, age, height, gender, or PWV—was found to be a strong predictor of long-term cardiovascular mortality.

In addition to the parameters already discussed, we found the HRs of the P compared to the N main groups and subgroups to be slightly but significantly lower, both at baseline and after beta-blockade. This differs from other studies that found an increased HR in prehypertensives compared to age-matched normotensives [27, 31]. The substantially different study conditions as well as differing ethnicity of the study groups could be reasons for these different findings. Regardless, by affecting the durations of systole and diastole, HR could directly affect f_0. However, because of the small differences in HR there is unlikely to be a discernible effect. In fact, we found no differences between any of the groups in f_0. HR differences are unlikely to impact the other parameters which differed between the N and P groups. Resistance is independent of time (and hence HR) because it is a ratio of two factors, both of which are time dependent. P_b is a magnitude that is independent of time, and P_b/P_f is also a ratio. Although we do not know the reason(s) for the lower HR in the P group, it might be related to the fact that, compared to age-matched normotensive counterparts, male but not female prehypertensives have been found to have abnormal autonomic control of heart rate and increased sympathovagal imbalance [27, 31]. The abnormal adrenergically mediated smooth muscle function could be another manifestation of autonomic dysfunction in prehypertension.

There are some limitations of our study that deserve discussion. First, we categorized patients based on the JNC 7 classification scheme in play at the time of the study [9]. According to the new 2017 guidelines [32], however, the patients in our P groups would now be reclassified into elevated or stage 1. Since blood pressure is a continuum any categorization is rather arbitrary. Hence, for the sake of simplicity and consistency we used the JNC 7 classification. Second, it is highly likely that the anxiety of the procedure caused the blood pressure reported herein of some, or many, of the patients to be higher than the precatheterization values on which they were categorized. We used this categorization to avoid the vagaries associated with categorizing based on the blood pressure at the time of the procedure but doing so may have made delineation of the categories a bit uncertain. Third, there are many noninvasive methods to estimate central aortic pressure and flow [3–6]. Each of these, however, entails an approximation, assumption, or mathematical transformation which has been validated but still engenders a certain degree of uncertainty. Instead, we used invasive measurements which are the most direct and accurate but which, admittedly, limited the study to a very small number of patients. The fact that we found statistically significant differences between groups, however, attests to the high quality, consistency, and robustness of the data. Fourth, our findings pertain to acute changes in young people in an environment far from normal. Whether similar results would be found with much larger numbers of people spanning a wider age range and in more normal settings clearly needs to be determined. Fifth, females comprised a smaller proportion than males in all groups so any specific gender effect would have been masked by the larger number of males. Additionally, there were proportionally more females in both the N compared to P main groups and subgroups. One parameter most likely to be affected by this gender imbalance is f_0 because, in general, women tend to have shorter body lengths than men and body length is a factor potentially affecting wave reflection time. Indeed, of the five shortest body lengths in our population, four were women. In addition, unlike men, women prehypertensives did not have abnormal autonomic control of heart rate nor sympathovagal

inhibition [27, 31]. Consequently, to directly examine this issue, we excluded females from all the main and subgroups and performed statistical analysis of f_0, as well as all the parameters listed in Table 3. This additional analysis revealed identical conclusions as when females were included (data not shown). Hence, the gender imbalance of our groups does not affect our conclusions.

Finally, with respect to future directions and therapeutic implications, our findings of increased wave reflections and subtle cardiac effects in young prehypertensives could be only the tip of the iceberg. It seems clear that further large-scale studies in prehypertensives, focusing specifically on hemodynamics during provocations such as exercise, are warranted to more clearly elucidate the pathophysiology of this condition.

Independent of our findings, there is also increasing evidence for deleterious effects of prehypertension. For example, one study found a familial disposition for hypertension across three generations, especially with early onset (< age 55) hypertension in grandparents [33]. Among young, normotensives parental hypertension was associated with increased arterial stiffness, wave reflections, and aortic augmentation index [34]. A four-year cumulative incidence of progression of nonhypertensives to hypertensives was found to increase stepwise across optimal, normal, and high normal blood pressure groups [35]. Prehypertension is statistically significantly associated with target organ damage, not only in the heart but also, especially, in the brain and kidneys [7]. Meta-analysis of a cohort study reported an elevated risk ratio of coronary heart disease in high normal pressure prehypertensives but not in the low normal pressure group [36]. Both gender and age-related increases in cardiovascular disease incidence in high normal pressure prehypertensives have been reported [37]. There appears to be a modest negative association between blood pressure and cognitive function [38]. Finally, a study of more than 2 million Israeli adolescents followed for an average of 17 years revealed that those in the normal-to-high-normal prehypertensive range had increased incidence of adult end-stage renal disease with a hazard ratio of 1.32 [39].

Current guidelines do not suggest treating prehypertensives. However, in light of the findings discussed above and if our results are borne out by further studies, there will be more compelling evidence of a need to reconsider our approach to prehypertension. This is especially germane since it appears that the hemodynamic abnormalities in young persons with prehypertension or established essential hypertension are still reversible. In particular, it might be worth considering alterations in lifestyle and the early use of specific classes of antihypertensive drugs that act to reduce wave reflections.

5. Conclusion

During diagnostic cardiac catheterization we measured detailed aortic hemodynamics in normotensives and age-matched prehypertensives in the baseline state and after acute beta-adrenergic blockade. In the baseline state the prehypertensives compared to the normotensives had elevated blood pressure, resistance, LVEDP, and wave reflections. Beta-adrenergic blockade increased resistance, LVEDP, and wave reflections in both groups. In subgroups selected so that there were no differences in blood pressure, the differences in LVEDP and wave reflections in the baseline state and after beta-blockade were still present. These baseline vascular abnormalities and responses to beta-blockade are very similar to those we previously reported in young persons with established, essential hypertension. Importantly, the elevated wave reflection in prehypertensives with the same blood pressure as normotensives suggests that this abnormality is not directly related to the level of blood pressure. Hence, these results support the notion that the elevation of blood pressure in hypertension may represent a later manifestation of an already abnormal vascular system rather than the vascular abnormalities being a result of the hypertension. Some implications for morbidity and treatment are discussed.

Data Availability

All of the available data are included in the article.

Conflicts of Interest

The authors declare that none of them had any financial or other conflicts of interest.

Acknowledgments

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Clinical Study

Safety and Efficacy of a New Renal Denervation Catheter in Hypertensive Patients in the Absent of Antihypertensive Medications: A Pilot Study

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Aim. The aim of present study was to determine the safety and efficacy of a new renal artery denervation system for treatment of hypertensive patients. *Methods*. Hypertensive patients with mean office systolic blood pressure ≥150mmHg and ≤180mmHg or an average of 24-hour ambulatory systolic blood pressure ≥145mmHg and ≤170mmHg after stopping hypertensive medications for 2 weeks or more were enrolled to undergo renal denervation (RDN) using a new RDN system. Changes in office blood pressure and mean 24-hour ambulatory blood pressure and safety were assessed after 6 months. *Results*. Fifteen patients underwent RDN and followed up for 6 months. At the 6-month follow-up, office systolic blood pressure decreased 11.5±9.9mmHg (P<0.01) and office diastolic blood pressure decreased 6.9±4.8mmHg (P<0.01); mean 24-hour ambulatory systolic blood pressure decreased 7.5±7.7mmHg (P<0.05) and mean 24-hour diastolic blood pressure decreased 3.3±4.7mmHg (P>0.05) compared to baseline values. There were no serious RDN-related adverse events during follow-up. *Conclusion*. Our results demonstrate that the new RDN system is safe and could significantly reduce blood pressure in hypertensive patients in the absence of antihypertensive medications. This trial is registered with ChiCTR1800017815.

1. Introduction

Hyperactivity of the sympathetic nervous system contributes an important role in the pathophysiology of hypertension. Renal denervation (RDN) is a new interventional treatment for resistant hypertension in recent years [1–4]. Recent clinical studies have shown that there are some controversies about the efficacy of RDN in the treatment of hypertension [5–7]. Ablation instruments are important quality assurances for RDN. Improvements in ablation catheters may further improve the quality of the procedure and reduce the operator's operational difficulty, thus potentially ensuring the efficacy of the procedure. This prospective, single-center, self-controlled study was designed to evaluate the efficacy and safety of a new RDN system [(ablator no.: GL-06E15WA, ablation catheter no: GL-6w (12mm), Shanghai Golden Leaf Medtech Company, Shanghai, China] in hypertensive patients without antihypertensive medication.

2. Methods

2.1. Subject Selection. Inclusion criteria are (1) age >18 and ≤75 years; (2) mean office systolic blood pressure ≥150mmHg and ≤180mmHg; or an average of 24-hour ambulatory systolic blood pressure ≥145mmHg and ≤170mmHg after stopping hypertensive medications for 2 weeks or more; (3) renal artery length ≥20mm. Exclusion criteria are (1) secondary hypertension; (2) glomerular filtration rate(GFR) <40mL/min; (3) unilateral or bilateral renal artery anatomy; (4) office SBP >180mmHg and/or diastolic blood pressure >110 mmHg after stopping hypertensive medication during the enrollment period. The study was approved by the Zhongda Hospital

FIGURE 1: Angiographic image of the renal denervation catheter applying circumferential ablations.

Ethics Committee of Southeast University (ethical approval number: 2015ZDSYLL077.0). NCT no. is ChiCTR1800017814. All enrolled patients signed informed consent.

2.2. RDN Procedure. RDN was performed by using the newly developed RDN system (GL-06E15WA ablator and GL-6W ablation catheter) developed by Shanghai Golden Leaf Medtech Company, Shanghai, China. The major features of this RND system are as follows: this system is easy to handle and supplies a 360° circular ablation with 6 electrodes, without affecting renal artery blood flow and the impact of respiratory movement on ablation is minimal. RDN procedure was performed as previously described [8]. Patients were taken to the catheterization laboratory to undergo the RDN procedure using conscious sedation. The ablation catheter should be advanced to the place where the electrode tip was fully visible in the renal artery and then pushed the electrode expansion button on the catheter handle to fit the electrode to the vessel wall (Figure 1) and then began the adherent diagnosis, observing the temperature change of the target ablation locations. The temperature was gradually increased to prove that adherence to the wall is suitable. The ablation parameter is set to 60°C and the ablation time is 120 seconds per point. After completion of 6 points ablation, the electrode expansion button was released to shrink the electrode tip and slowly returned to the guide sheath. Fentanyl citrate 1-2ug/kg.h was maintained intravenously for analgesia treatment. Postoperative antiplatelet therapy (aspirin 100mg po qd; clopidogrel 75mg po qd) was applied for 4 weeks after RDN.

Study Endpoints. Mean office blood pressure and 24-hour ambulatory blood pressure, remote blood pressure monitoring data, and complications at 6 months were followed up. Safety: the occurrence of study-related adverse events during the trial, especially renal function indicators and renal artery complications. Adverse events or serious adverse events that may occur during or after the procedure: renal artery stenosis, renal artery dissection, thromboembolism, artery puncture site complications, arteriovenous fistula, sepsis, and other possible adverse reactions during the period [2].

2.3. Statistical Analysis. The continuous data were expressed as mean±standard deviation. Differences from baseline to the 6-month follow-up assessment were tested with the use of paired t-tests. P <0.05 was considered as statistically significant.

3. Result

3.1. Baseline Characteristics. A total of 15 patients (14 male) underwent RDN and all finished the 6-month follow-up. The mean age was 39.0±7.0 years, average heart rate was 70±2.6 beats/min, and the average GFR was 127.8±24.5 mL/min.

3.2. Efficacy. The office systolic blood pressure was 158.2 ±6.4mmHg at baseline, 146.7±11.6mmHg at 6 months after RDN. The office diastolic blood pressure was 100.3± 8.8mmHg at baseline and 93.4±7.2mmHg at 6 months after RDN. Office systolic blood pressure decreased 11.5± 9.9mmHg (P<0.01) and diastolic blood pressure decreased 6.9±4.8mmHg (P<0.01) at 6 months post RDN compared to baseline levels (Table 1).

The mean 24-hour ambulatory systolic blood pressure was 154.5±10.7mmHg at baseline and 147.0±12.0 at 6 months after RDN (reduction was -7.5±7.7mmHg compared to baseline, P<0.05). The mean 24-hour ambulatory diastolic blood pressure at baseline was 97.5±8.1mmHg and 94.2±9.2 mmHg at 6 months after RDN (reduction was -7.5±7.7 mmHg compared to baseline, P=0.055)(Table 2).

3.3. Safety. Renal function and the average heart rate were similar between baseline and 6-month follow-up. No complications such as renal artery stenosis and renal artery dissection were observed during the 6-month follow-up in this patient cohort.

4. Discussion

RDN is an interventional method used for the treatment of refractory hypertension, but the real world and clinical trial efficacy remains controversial. The study of SIMPLICITY HTN-1 and simplicity HTN-2 using SIMPLICITY™ catheter ablation showed that RDN is safe and effective for refractory hypertension[6, 7], but in the prospective, single-blind, randomized, sham-controlled SIMPLICITY HTN-3 trial, RDN failed to significantly reduce blood pressure in patients with refractory hypertension [9]. The following factors might be responsible for the controversial results: (1) insufficient understanding on the working mechanisms of RDN; (2) study design limitations: there is a need to include randomized double-blind, sham-surgery group as control group, and multicenter clinical trials; secondary hypertension should be excluded; the study endpoints should be identical and at best to use the 24-hour ambulatory blood pressure; (3) surgical factors: the learning curve of the operation and the experience of the operators should be comparable and considered on the comparison of various study results. Last but least the efficacy of various ablation catheters used should be taken into account when evaluating the RDN efficacy [10–12]. Moreover, there are also some problems related to the

Table 1: Changes in office blood pressure.

	Systolic blood pressure		Diastolic blood pressure	
	Mean blood pressure	Mean change from baseline	Mean blood pressure	Mean change from baseline
Baseline	158.2±6.4		100.3±8.8	
6 months	146.7±11.6	−11.5±9.9[a]	93.4±7.2	−6.9±4.8[b]

[a]$P <0.01$; [b]$P <0.01$ versus baseline.

Table 2: Changes in Mean 24-hour ambulatory blood pressure.

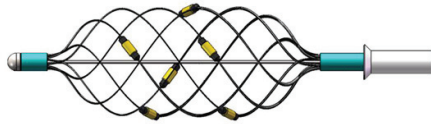|	24-hour ambulatory systolic blood pressure		24-hour ambulatory diastolic blood pressure	
	Mean pressure	Mean change from baseline	Mean pressure	Mean change from baseline
Baseline	154.5±10.7		97.5±8.1	
6 months	147.0±12.0	-7.5±7.7[a]	94.2±9.2	-3.3±4.7[b]

[a]$P <0.05$,[b]$P =0.055$

Figure 2: 6-point reticular electrodes ablation catheter.

RDN procedures: (1) the degree of ablation on the nerve, temperature on ablation point, and ablation time might all affect the therapeutic effect. Therefore, the RDN system needs to be constantly explored and improved; an ideal RDN ablation catheter should have the following characteristics: (1) the operation should be more simple; (2) the level of dependence on the operator should be reduced to minimum; and (3) the time to achieve the maximum nerve denervation effect should be reduced to the minimum.

The Symplicity™ catheter system is a widely used RDN system in clinical practice now, but this system has several limitations: (1) the catheter has only one electrode, which leads to long ablation time; (2) the selection of vascular ablation site by unipolar electrode is relatively difficult; (3) it is difficult to ablate deep renal sympathetic nerve, since this catheter only possesses low radio frequency power and limited penetration depth. So these deficiencies are likely to be responsible for the uncertainty of clinical trial results. In order to solve the core problem of RND, the latest SPYRAL HTN-OFF MED study used a different innovative Symplicity Spyral multielectrode catheter, which has 4 electrodes, and can ablate 4 locations at the same time from different locations, and preliminary results showed that RDN with this catheter can significantly reduce blood pressure in hypertensive patients in the absence of antihypertensive medications [13, 14].

The RDN in our study is achieved through a 6-point reticular electrodes catheter ablation system, which is simple in operation and easy to locate due to the 360° annular ablation design. Its basket-shaped design also guaranteed the impact on renal arterial blood flow, and it was suitable for ablating vessels with different morphologies and sizes. The real time impedance measurement function and temperature monitoring function during RDN procedure are also available to assist the operator to control the efficacy and quality of RDN process (Figure 2).

In conclusion, our preliminary study results show that the new RDN system used in this study is safe and can effectively reduce the blood pressure in primary hypertensive patients in the absence of antihypertensive medication.

Data Availability

Our research data will be shared in the clinical trial management public platform: ResMan.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Prevalence, Awareness, and Control of Hypertension in Greater Beirut Area, Lebanon

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Background. Hypertension (HTN) has been identified as the leading risk factor for mortality and the third cause of disability worldwide. Lebanon has witnessed a threefold increase in the prevalence of HTN in the past decade. The timely exploration and detection of the factors contributing to a higher prevalence of the disease among the Lebanese population is fundamental. The objectives of this study were to assess the prevalence, awareness, and control rates of HTN in Greater Beirut Area in Lebanon and to identify their respective predictors. *Methods.* A representative sample of 501 participants aged 18-79 years residing in Greater Beirut Area was examined. Data collection form was filled up, through interviews, physical exams, and lab tests. The analysis was done for three defined outcomes: blood pressure status (normotensive, prehypertension, and hypertension), unaware HTN, and uncontrolled HTN. These were compared for the various associated predictors. *Results.* The sample consisted of 64.3% women and mean age 45.4 ± 15 years and the subjects were predominantly from low educational income levels. The results showed that 36.4% of the study participants were hypertensive, 25.3% were prehypertensive, and 38.2% had optimal blood pressure, while the awareness rate was 65.4% and control rate was 61%. The independent predictors of HTN were age, gender, marital status, T2D, body fat, triglyceride (positive correlates), and income level (negative correlate). Moreover, unawareness of HTN was common among older age, men, single participants, and the obese. We could not identify any factor related to uncontrolled HTN. *Conclusion.* The trend in the prevalence of HTN in Greater Beirut Area is found to be consistent and relatively high, yet there was an observed improvement in the awareness and control of the disease. Public health measures on a national level are urgently needed to curb the increasing prevalence of HTN, achieve primary prevention, and better control the disease.

1. Introduction

HTN has been identified as the leading risk factor for mortality and is ranked as the third cause of disability worldwide [1]. Globally, it has been estimated that 9.4 million deaths annually are due to complications of HTN, such that 45% of deaths are due to heart diseases and 51% of deaths are due to stroke [2]. Therefore, HTN is a driving factor of the global burden of cardiovascular diseases and its complications.

Moreover, this is expected to increase as projections estimate that there will be a 30% increase in the prevalence of HTN by the year 2025 [2]. Importantly, three-quarters of the world's hypertensive population will reside in the low and middle income countries (LMICs) within the next decade [1].

In 2008, it was estimated that, globally, 4 in 10 adults over the age of 25 years and at the prime of their productivity were hypertensive [3]. Consequently, the burden is limited not only to the individual's health, but also to the significant economic

burden and loss [2]. The WHO estimated that 3.76 trillion dollars will be an output lost and spent on cardiovascular diseases in the LMICs during the period 2011-2025 [2]. Hence, HTN is majorly affecting the nations' economic development of the LMICs due to the loss of income and the high costs of medical care [3].

The fact that the populations in the LMICs are bearing one of the highest burdens of the disease can be owed to the alarming rates of demographic changes including the growth and ageing of the populations, urbanization, and globalization [4]. These changes led to shifts in the lifestyle habits and behaviors, demonstrated mainly by the ongoing nutritional transition, the adoption of westernized high energy dense diets, and the reduced physical activity at the workplace and at leisure [4, 5].

The Arab world reported a higher crude prevalence of HTN (29.5%) when compared to other regions of the world such as the sub-Saharan Africa (27.6%) and the USA (28%) [6]. Lebanon, a small middle income Arab country, was reported to have higher prevalence rates of HTN when compared to its adjacent countries, such as Palestine and Egypt [7]. Findings of recent studies in Lebanon have showed that HTN affects one-third of the Lebanese population and an additional 30% are prehypertensive [7]. Of more concern is the observed increasing secular trend whereby Lebanon has witnessed a threefold increase in the prevalence of HTN during the past decade [4, 7, 8]. While the awareness and control rates of HTN in Lebanon (53%, 27%, respectively) are found to be better than the adjacent countries [7] yet these rates remain low compared to the high income ones [9].

Epidemiological data has revealed the need for increased awareness of HTN especially in low and middle income countries where the public awareness of the disease is moderately dismal [10, 11] as well as for abundant research on the management of the disease. The timely exploration of the burden of hypertension in the Lebanese community is fundamental, as it serves in guiding healthcare policy makers and public health providers to implement effective and tailored interventions for better management of the disease. Hence, this study aimed at (1) assessing the prevalence of HTN and pre-HTN amongst adults in Lebanon; (2) assessing the awareness and control rates of HTN; (3) investigating the factors associated with HTN, unaware HTN, and uncontrolled HTN in this population.

2. Methods

2.1. The Study Design and Target Population. This was a community based cross-sectional study conducted in 2014 in Greater Beirut Area (GBA). The study recruitment was done at the American University of Beirut (AUB) over a 3-month period from March until May 2014. The study included Lebanese adults aged 18-79 years and residing in GBA. It excluded vulnerable populations, mainly pregnant and lactating women, dialysis patients, and subjects with mental disabilities. The study was approved by the Institutional Review Board of AUB. A study by Nasrallah et al. reported the prevalence of type 2 diabetes in the Lebanese population from

the collected data [12]. The study explained the methodology of the project elaborated below [12].

2.2. Sampling Strategy. The selection criteria were based on multistage probability sampling. First, the districts of Central Administrative Beirut in addition to areas in the districts of Chouf, Aley, Baabda, Metn, and Keserwan were selected as clusters. Second, within each selected cluster, neighborhoods were selected to represent the make-up of the areas, followed by the selection of the households which was based on a systematic random sampling according to the estimated number of buildings in the neighborhood. Finally, sampling a primary respondent within each household based on the most recent birthday was done. The objectives of the study along with the methods were clearly explained to the selected participants who accepted to get enrolled. Those who agreed on the objectives and conditions had signed an informed consent.

2.3. Data Collection. Information collected from subjects included (1) demographic and socioeconomic data: age, gender, marital status, education, and income level; (2) lifestyle-related data: smoking (current smoker defined as any daily smoking, regardless of the number of cigarettes or water-pipe), alcohol intake (defined as any intake), caffeine intake, and being physical active, assessed as (yes/no); (3) medical history: coronary artery disease and diabetes mellitus; (4) anthropometric measures: waist circumference and waist-to-hip ratio using a standardized method [13] and body composition using bioimpedance analyzer (Inbody Body Composition Analyzer, In body 230); sitting blood pressure and heart rate were obtained twice at 10-minute intervals using a digital sphygmomanometer; and (5) laboratory measures: fasting glucose, HbA_{1C}, lipid profile, CRP, sodium urine, and potassium urine. (6) Dietary assessment was performed using an 80-item culture-specific semiquantitative food frequency questionnaire (QFFQ) that estimated food and beverage intakes over the past year [14]. The daily energy and macronutrient intake levels were computed using the food composition database of the Nutritionist Pro Software (Axxya Systems LCC 2016, Nutritionist Pro™ version 6.3.0. Stafford) [14, 15].

2.4. Outcome Related Variables. According to the thresholds of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Seven (JNC 7) and the (JNC 8) guidelines for the management of hypertension in adults, the participants were classified as follows:

(i) Hypertensive individuals: defined as those with SBP ≥140 mm Hg and/or DBP ≥ 90 mmHg [16] or those who have been informed of being diagnosed with HTN.

(ii) Prehypertensive individuals: defined as those who have not been informed of HTN diagnosis and with SBP 120- 139 mm Hg and/or DBP 80-89 mm Hg [16] and not on pharmacologic treatment.

(iii) Normotensive individuals: defined as those who have not been informed of HTN diagnosis and with SBP

< 120 mm Hg and DBP < 80 mm Hg [16] and not on pharmacologic treatment.

(iv) Aware individuals: defined as those who have been informed of HTN diagnosis [17].

(v) Unaware individuals: defined as those who have never been informed of HTN diagnosis and with SBP ≥140 mm Hg and/or DBP ≥ 90 mm Hg.

(vi) Controlled HTN: defined as SBP < 140 mmHg for individuals below the age of 60; SBP < 150 mm Hg for individuals above the age of 60 years and DBP < 90 mmHg as a result of pharmacologic treatment among the aware hypertensive [18].

(a) Treated individuals: defined as those who were aware of being hypertensive and are on pharmacologic treatment

2.5. Statistical Analysis. Descriptive statistics were conducted for the overall characteristics of the study population through presenting the numbers and percent for the categorical variables and means and standard deviations for the continuous ones. Inferential bivariate analysis was carried out where Chi square or Fisher exact tests were used for the categorical and binary factors, as appropriate. Independent t-test and one-way ANOVA tests were conducted for the continuous variables. Results were presented by the p-values in addition to the descriptive statistics for each of the outcome groups identified. Multiple and multinomial logistic regression were carried out to adjust for potential confounding and/or interaction effect of variables under study. The stepwise approach was used to choose the best model. The results were presented by the odds ratios and 95% confidence intervals (CI). P-value < 0.05 was set as an indicator of statistical significance. The data analysis was done on two types of software: SPSS 22 and STATA 13.

3. Results

A total of 501 subjects participated in the study. The sample consisted of 322 women (64.3%) and 179 men (35.7%), with a mean age of 45.4 ± 15.0 years. Approximately 10% of the study participants reported a monthly income above 2000 USD per household and university level of education. The lifestyle habits results showed that 43% of the participants were current cigarettes smokers, 28.3% were current nargileh smokers, and 19% were current alcohol drinkers. The majority of the study participants reported drinking coffee (80.4%) and engaging in physical activity (84.2%) (Table 1). The overall prevalence of HTN in GBA was 36.4%, 25.3% were pre-HTN, and the rest were normotensive (38.2%). The awareness rate among the hypertensive participants was 65.4% while the control rate amongst those who are on treatment and aware of being hypertensive was estimated at 61.2%.

3.1. Predictors of Pre-HTN and HTN. Table 2 presents the differences in the characteristics of the participants among the three BP groups (normotensive, pre-HTN, and HTN).

The results showed that there was an increase in the mean age with the increase in BP categories, such that the mean age was 40.24 ± 12.8, 41.6 ± 14.2, and 53.6 ± 14.2 years for the normotensive, pre-HTN, and hypertensive, respectively (p-value <0.0001). Males were found to be more hypertensive (37.4%) than normotensive (25.1%) unlike women (p-value< 0.0001). Significant difference in the income level between the BP groups was detected as higher prevalence of HTN (51.2%) was observed among those who receive <600 USD compared to the normotensive (25.3%); this prevalence (15.0%) is lower among those who receive 1000-2000 USD compared to the normotensive (27.6%). Similar results were observed for the educational level.

BMI and abdominal obesity were found to be significant correlates. The percentage of the obese individuals increased significantly and gradually among the three groups (23.3% for the normotensive, 45.6% for the pre-HTN, and 59.3% for the hypertensive individuals). Furthermore, the results showed significant differences in the mean of the macronutrients (carbohydrates, total fat, and the saturated fats in addition to the total energy) among the different groups, where the highest mean of each of the mentioned macronutrients was among the pre-HTN group while the lowest was among the hypertensive group when compared to the normotensive (p-value <0.05) (Table 2).

Results of the logistic regression analyses showed that the main factors that were significantly associated with HTN were age, income level, T2D, triglyceride, and CRP (Table 3). Older age groups were at higher odds of having HTN in comparison to participants below the age of 30 years. The odds increased up to 3.53 (95% CI: 0.94-11.72) for the age group 51-60 years and to 17.91 (95% CI: 4.97- 64.45) for those above the age of 60 years. Interestingly, higher income levels were associated with lower odds of developing HTN, yet the only significant result was among those who earn more than 2000 USD per household with an OR = 0.22 (95% CI: 0.07-0.88). Besides, T2D was found to be a positive correlate which increases the odds of having HTN by 2.4 (95% CI: 1.08-7.02). Similarly, a positive association was obtained with the CRP and TG levels (OR = 1.46; 95% CI: 1.08-2.01) (OR = 1.04; 95% CI: 1.01-1.08). On the other hand, urinary potassium and HDL were the only predictors that were significantly associated with pre-HTN. Urinary potassium was a negative correlate of pre-HTN (p-value = 0.01), while HDL was found to be a positive one (p-value = 0.003).

The logistic regression analysis results (Table 3) showed that gender and body fat were the two common positive predictors for both the HTN and pre-HTN categories with almost equal strength of associations. The odds of being hypertensive (OR = 4.78; 95% CI: 2.25-11.11) and pre-HTN (OR = 3.71; 95% CI: 2.56-9.72) was higher among males compared to females. Similarly, for every unit increase in body fat, the odds of HTN and pre-HTN increased by 1.08 (95% CI: 1.05-1.12) and by 1.05 (95% CI: 1.02-1.09), respectively.

3.2. Predictors of Unaware HTN. Table 4 presents the differences in the characteristics between the normotensive participants and the unaware hypertensive. The bivariate

TABLE 1: Baseline characteristics of the study sample.

			N (%)
Total sample			501
Demographic	Age	≤ 30	107 (21.4%)
		31-40	78 (15.6%)
		41-50	118 (23.6%)
		51-60	123 (24.6%)
		> 60	75 (14.9%)
	Age	mean ± SD	45.4 ± 15.0
	Gender	Males	179 (35.7%)
		Females	322 (64.3%)
	Marital status	Married	332 (66.3%)
		Single	98 (19.6%)
		Others	71 (14.2%)
Socioeconomic	Income	<600$	153 (33.8%)
		600-999.9$	170 (37.5%)
		1000-2000$	90 (19.9%)
		>2000$	40 (8.8%)
	Education	No school /Primary	181 (36.3%)
		Intermediate/Secondary/Technical	263 (52.8%)
		University degree	54 (10.8%)
Lifestyle habits	Smoking cigarettes	Never	236 (47.1%)
		Current	216 (43.1%)
		Ex-smoker	49 (9.8%)
	Narghileh Smoking	Never	311 (62.1%)
		Current	142 (28.3%)
		Ex-smoker	48 (9.6%)
	Alcohol drinking	Never	372 (74.3%)
		Current	95 (19.0%)
		Ex-smoker	34 (6.8%)
	Coffee drinking		403 (80.4%)
	Physical activity		422 (84.2%)

results showed that unawareness was more common among older people, males, lower income level, obese, and those with higher levels of lipid profile. The mean age of the unaware hypertensive (47.6 ± 16.6 years) was significantly higher than that of the normotensive (40.2 ± 12.8 years) with a p-value = 0.002. Moreover, the income level was found to be significantly associated with the unawareness of the disease, with a p-value = 0.03. Interestingly, obesity was found to be more common among the unaware (58.7%) (p-value <0.0001) compared to the normotensive ones (23.0%) and with a higher mean of body fat (32.9 ± 12.3) than the normotensive (24.9 ± 9.7) (p-value = 0.001). Significant association at the bivariate level was also obtained between blood glucose, HbA1c, CRP, cholesterol, triglyceride, and LDL such that the mean of each mentioned lab test was higher among the unaware patients. Yet, the mean of the glomerular filtration rate was lower among the unaware patients (95.8 ± 21.1) than those who are normal (104.9 ± 22.8) (p-value = 0.006) which can be indicative of chronic kidney disease.

Upon adjustment, age was found to be the significant predictor with the strongest association for the unawareness.

Significant results were reported among those who are above the age of 60 years, such that the odds for an older person to be unaware of being hypertensive increased up to OR = 7.36 as compared to those ≤ 30 years old (p-value = 0.01). Also, males were found to be at higher odds of being unaware of the disease with an OR = 5.15 (95% CI 2.16-12.25; p-value <0.0001) and the same applies to the single participants with an OR = 4.55 (95% CI: 1.16-17.76; p-value = 0.02). Higher BMI was more common among the unaware patients such that the odds of being unaware hypertensive patient among the obese were found to be 7 times more likely when compared to those with normal weight (OR = 6.83, 95% CI: 2.59-22.01; p<0.0001) (Table 5).

3.3. Predictors of Uncontrolled HTN. Table 6 presents the differences in the characteristics of the controlled hypertensive patients and the uncontrolled ones. The results showed that hypertensive males were more likely to be uncontrolled (37.5%). Similarly, obese participants were more uncontrolled (70.0%) compared to the controlled (79.4%). Yet, none

TABLE 2: The association of demographic, socioeconomic, lifestyle, anthropometric, dietary intake, and medical history and laboratory tests with BP.

Variables			Normotensive N = 191 38.2%	Pre-HTN N = 127 25.3%	HTN N = 182 36.4%	p-value
	Age	Mean (± sd)	40.2 ± 12.8	41.6 ± 14.2	53.6 ± 14.2	<0.0001*
Demographic	Age	≤ 30	51 (26.7%)	36 (28.3%)	19 (10.4%)	<0.0001*
		31-40	42 (22.0%)	23 (18.1%)	13 (7.1%)	
		41-50	57 (29.8%)	32 (25.2%)	29 (15.9%)	
		51-60	34 (17.8%)	23 (18.1%)	66 (36.3%)	
		> 60	7 (4.0%)	13 (10.2%)	55 (30.2%)	
	Gender	Females	143 (74.9%)	64 (50.4%)	114 (62.6%)	<0.0001*
		Males	48 (25.1%)	63 (49.6%)	68 (37.4%)	
	Marital status	Married	138 (72.3%)	80 (63.0%)	113 (62.1%)	<0.0001*
		Single	39 (20.4%)	35 (27.6%)	24 (13.2%)	
		Others	14 (7.3%)	12 (9.4%)	45 (24.7%)	
Socioeconomic	Income	<600$	44 (25.3%)	27 (22.9%)	82 (51.2%)	<0.0001*
		600-999.9 $	64 (36.8%)	58 (49.2%)	47 (29.4%)	
		1000-2000$	48 (27.6%)	18 (15.3%)	24 (15.0%)	
		>2000$	18 (10.3%)	15 (12.7%)	7 (4.4%)	
	Educational	No school /Primary	50 (26.6%)	44 (34.6%)	87 (47.8%)	<0.0001*
		Intermediate/Secondary/Technical	114 (60.6%)	65 (51.2%)	83 (45.6%)	
		University degree	24 (12.8%)	18 (14.2%)	12 (6.6%)	
	Cigarette smoking	Never	90 (47.1%)	59 (46.5%)	86 (47.3%)	0.09
		Current	89 (46.6%)	57 (44.9%)	70 (38.5%)	
		Ex-smoker	12 (6.3%)	11 (8.7%)	26 (14.3%)	
	Narghileh smoking	Never	108 (56.5%)	78 (61.4%)	124 (68.1%)	0.11
		Current	62 (32.5%)	40 (31.5%)	40 (22.0%)	
		Ex-smoker	21 (11.0%)	9 (7.1%)	18 (9.9%)	
Lifestyle habits	Coffee drinking	No	41 (21.5%)	29 (22.8%)	27 (14.8%)	0.14
		Yes	150 (78.5%)	98 (77.2%)	155 (85.2%)	
	Alcohol drinking	Never	151 (79.1%)	85 (66.9%)	135 (74.2%)	0.08
		Current	31 (16.2%)	33 (26.0%)	31 (17.0%)	
		Ex-drinker	9 (4.7%)	9 (7.1%)	16 (8.8%)	
	Physical activity	None	27 (14.1%)	21 (16.5%)	31 (17.0%)	0.71
		Any activity	164 (85.9%)	106 (83.5%)	151 (83.0%)	
Anthropometric measurements	BMI	Normal	66 (34.9%)	34 (27.2%)	16 (8.8%)	<0.0001*
		Overweight	79 (41.8%)	34 (27.2%)	58 (31.9%)	
		Obese	44 (23.3%)	57 (45.6%)	108 (59.3%)	
	Abdominal obesity – waist circumference		83 (43.7%)	59 (46.8%)	136 (74.7%)	<0.0001*

TABLE 2: Continued.

Variables			Normotensive N = 191 38.2%	Pre-HTN N = 127 25.3%	HTN N = 182 36.4%	p-value
	Abdominal obesity- waist to hip ratio		152 (80.4%)	82 (65.6%)	149 (82.3%)	0.001l*
	Body fat	Mean (± sd)	24.9 ± 9.8	27.5 ± 12.3	33.4 ± 11.1	<0.0001*
Dietary intake	Total energy –Kcal	Mean (± sd)	3291.0 ± 1532.3	3714.2 ± 1534.5	3057.4 ± 1473.2	0.01*
	Total protein (g/d)	Mean (± sd)	108.9 ± 77.2	118.7 ± 54.2	101.9 ± 60.1	0.14
	Carbohydrates (g/d)	Mean (± sd)	390.5 ± 224.2	438.8 ± 268.7	374.9 ± 211.8	0.05*
	Total fat (g/d)	Mean (± sd)	144.4 ± 89.4	159.3 ± 96.1	129.7 ± 78.1	0.01*
	Saturated fat (g/d)	Mean (± sd)	38.5 ± 25.4	43.65 ± 31.8	32.9 ± 21.3	0.002*
	% of calories from carbohydrates	Mean (± sd)	48.8 ± 8.7	48.5 ± 7.8	49.5 ± 8.7	0.57
	% of calories from proteins	Mean (± sd)	13.2 ± 3.9	12.9 ± 2.6	13.5 ± 3.0	0.40
	% of calories from fat	Mean (± sd)	38.9 ± 7.8	38.9 ± 7.6	37.9 ± 8.7	0.28
	% of calories from saturated fat	Mean (± sd)	10.2 ± 2.7	10.2 ± 2.8	9.5 ± 2.7	0.03*
Medical History	Cardiac catheterization		10 (5.2%)	6 (4.7%)	29 (15.9%)	<0.0001*
	Previous heart attack		7 (3.7%)	2 (1.6%)	13 (7.1%)	0.05*
	Family history	CAD	70 (36.6%)	56 (44.1%)	63 (34.6%)	0.22
		T2D	9 (4.7%)	12 (9.4%)	54 (29.7%)	<0.0001*
Lab tests	Glucose	Mean (± sd)	100.3 ± 28.0	107.5 ± 32.7	127.1 ± 56.6	<0.0001*
	HbA1c	Mean (± sd)	5.5 ± 0.8	5.8 ± 1.1	6.4 ± 1.7	<0.0001*
	CRP	Mean (± sd)	10.2 ± 7.2	11.3 ± 8.2	14.76 ± 13.0	<0.0001*
	Cholesterol	Mean (± sd)	182.2 ± 37.5	182.8 ± 40.3	192.3 ± 50.1	0.052
	TG	Mean (± sd)	118.8 ± 68.8	143.3 ± 145.9	164.3 ± 88.4	<0.0001*
	HDL	Mean (± sd)	50.8 ± 14.8	51.5 ± 16.4	46.9 ± 13.1	0.01*
	LDL	Mean (± sd)	107.0 ± 32.9	105.1 ± 35.4	113.3 ± 48.3	0.12
	Sodium urine	Mean (± sd)	126.2 ± 47.9	125.6 ± 57.4	113.7 ± 48.3	0.03*
	Potassium urine	Mean (± sd)	79.3 ± 34.9	69.6 ± 31.8	76.2 ± 32.9	0.03*
	GFR (Ml/min/1.73 m^2)	Mean (± sd)	104.9 ± 22.8	102.3 ± 23.9	93.0 ± 26.1	<0.0001*

TABLE 3: The multinomial logistic regression model for the BP groups.

		Normotensive	Pre-HTN	OR (95% CI) Pre-HTN/Normotensive	HTN	OR (95% CI) HTN/Normotensive
Age	≤ 30	51 (26.7%)	36 (28.3%)	Ref	19 (10.4%)	Ref
	31-40	42 (22.0%)	23 (18.1%)	1.04 (0.43-2.59)	13 (7.1%)	1.39 (0.46-4.19)
	41-50	57 (29.8%)	32 (25.2%)	1.25 (0.50-3.02)	29 (15.9%)	1.72 (0.57-5.19)
	51-60	34 (17.8%)	23 (18.1%)	1.39 (0.43-3.04)	66 (36.3%)	4.93 (1.67-14.51)
	≥ 60	7 (3.7%)	13 (10.2%)	3.53 (0.94-11.72)	55 (30.2%)	17.91 (4.97- 64.45)
Gender	Females	143 (74.9%)	64 (50.4%)	Ref	114 (62.6%)	Ref
	Males	48 (25.1%)	63 (49.6%)	3.71 (2.56-9.72)	68 (37.4%)	4.78 (2.25-11.11)
Marital Status	Married	138 (72.3%)	80 (63.0%)	Ref	113 (62.1%)	Ref
	Single	39 (20.4%)	35 (27.6%)	1.82 (0.71-4.41)	24 (13.2%)	3.57 (1.02-8.09)
	Others	14 (7.3%)	12 (9.4%)	1.15 (0.43-2.96)	45 (24.7%)	2.22 (0.95-5.16)
Income level	<600 $	44 (25.3%)	27 (22.9%)	Ref	82 (51.2%)	Ref
	600-999.9$	64 (36.8%)	58 (49.2%)	1.56 (0.83-3.14)	47 (29.4%)	0.67 (0.38-1.42)
	1000-2000$	48 (27.6%)	18 (15.3%)	0.64 (0.29-1.44)	24 (15.0%)	0.55 (0.25-1.19)
	>2000$	18 (10.3%)	15 (12.7%)	1.03 (0.38-2.98)	7 (4.4%)	0.22 (0.07-0.88)
T2D		9 (4.7%)	12 (9.4%)	1.21 (0.44-3.87)	54 (29.7%)	2.41 (1.08-7.02)
Abdominal obesity (waist to hip ratio)		152 (80.4%)	82 (65.6%)	0.54 (0.21-1.43)	149 (82.3%)	1.09 (0.41-2.89)
Body fat	Mean (sd)	24.9 ± 9.8	27.5 ± 12.3	1.05 (1.02-1.09)	33.4 ± 11.1	1.08 (1.05-1.12)
Urinary potassium (10 units)	Mean (sd)	79.3 ± 34.9	69.6 ± 31.8	0.89 (0.98-0.99)	76.2 ± 32.9	0.95 (0.98-1.003)
TG (10 units)	Mean (sd)	118.8 ± 68.8	143.3 ± 145.9	1.01 (0.99-1.01)	164.3 ± 88.4	1.04 (1.01-1.08)
HDL (10units)	Mean (sd)	50.8 ± 14.8	51.5 ± 16.4	1.37 (1.01-1.05)	46.9 ± 13.1	1.15 (0.93-1.42)
CRP (10 units)	Mean (sd)	10.2 ± 7.2	11.3 ± 8.2	1.17 (0.82-1.62)	14.76 ± 13.0	1.46 (1.08-2.01)

TABLE 4: The association of demographic, socioeconomic, lifestyle, anthropometric, dietary intake, and medical history and laboratory tests with unaware hypertensive.

Variables N = 254			Normotensive N = 191 (75.2%)	Unaware HTN N = 63 (24.8%)	P-value
	Age	Mean (± sd)	40.2 ± 12.8	47.6 ± 16.6	0.002
		≤ 30	51 (26.7%)	16 (25.4%)	0.002
	Age	31-40	42 (22.0%)	5 (7.9%)	
		41-50	57 (29.8%)	8 (12.7%)	
		51-60	34 (17.8%)	20 (31.7%)	
Demographics		≥ 60	7 (3.7%)	14 (22.2%)	
	Gender	Males	48 (25.1%)	34 (54.0%)	<0.0001
		Females	143 (74.9%)	29 (46.0%)	
	Marital Status	Married	138 (72.3%)	32 (50.8%)	0.002
		Single	39 (20.4%)	18 (28.6%)	
		Others	14 (7.3%)	13 (20.6%)	
	Income Level	<600 $	44 (25.3%)	25 (44.6%)	0.03
		600-999.9$	64 (36.8%)	16 (28.6%)	
Socioeconomic		1000-2000$	48 (27.6%)	9 (16.1%)	
		>2000$	18 (10.3%)	6 (10.7%)	0.33
	Education Level	No school/Primary	50 (26.6%)	23 (36.5%)	
		Intermediate/Secondary/Technical	114 (60.6%)	33 (52.4%)	
		University degree	24 (12.8%)	7 (11.1%)	
	Cigarette smoking	Never	90 (47.1%)	28 (44.4%)	0.025
		Current	89 (46.6%)	24 (38.1%)	
		Ex-smoker	12 (6.3%)	11 (17.5%)	
	Narghileh Smoking	Never	108 (56.5%)	37 (58.7%)	0.63
		Current	62 (32.5%)	17 (27.0%)	
Lifestyle habits		Ex-smoker	21 (11.0%)	9 (14.3%)	
	Coffee drinking	No	41 (21.5%)	12 (19.0%)	0.68
		Yes	150 (78.5%)	51 (81.0%)	
	Alcohol drinking	Never	151 (79.1%)	45 (71.4%)	0.41
		Current	31 (16.2%)	13 (20.6%)	
		Ex-drinker	9 (4.7%)	5 (7.9%)	
	Physical Activity	None	27 (14.1%)	9 (14.3%)	0.97
		Yes	164 (85.9%)	54 (85.7%)	
	BMI	Normal	66 (34.6%)	10 (15.9%)	<0.0001
		Overweight	79 (41.4%)	16 (25.4%)	
Anthropometric Measurements		Obese	44 (23.0%)	37 (58.7%)	
	Waist Circumference- Abdominal Obesity	No	107 (56.3%)	23 (36.5%)	0.005
		Yes	83 (43.7%)	40 (63.5%)	
	Waist to hip ratio- Abdominal Obesity	No	37 (19.6%)	13 (21.0%)	0.82
		Yes	152 (80.4%)	49 (79.0 %)	
	Body Fat	Mean (± sd)	24.9 ± 9.7	32.9 ± 12.3	0.001

Table 4: Continued.

Variables N = 254			Normotensive N = 191 (75.2%)	Unaware HTN N = 63 (24.8%)	P-value
Dietary intake	Total Energy - Kcal	Mean (± sd)	3134.0 ± 1532.3	3268.6 ± 1487.6	0.55
	Total Protein (g/d)	Mean (± sd)	104.7 ± 71.2	107.7 ± 55.8	0.76
	Carbohydrates	Mean (± sd)	372.5 ± 174.1	396.9 ± 175.2	0.34
	Total Fat	Mean (± sd)	137.4 ± 76.5	139.7 ± 70.62	0.84
	Saturated Fat	Mean (± sd)	36.7 ± 22.4	37.7 ± 20.4	0.76
	% of calories from carbs	Mean (± sd)	48.8 ± 8.7	48.9 ± 7.6	0.88
	% of calories from proteins	Mean (± sd)	13.2 ± 3.9	13.3 ± 2.9	0.73
	% of calories from fat	Mean (± sd)	38.9 ± 7.9	38.3 ± 7.4	0.56
	% of calories from saturated fat	Mean (± sd)	10.2 ± 2.7	10.3 ± 3.0	0.72
Medical History	Cardiac catheter		10 (5.2%)	2 (3.2%)	0.73
	CAD / Previous heart attack		7 (3.7%)	2 (3.2%)	1.00
	Family history		70 (36.6%)	24 (38.1%)	0.83
	T2D		9 (4.7%)	6 (9.5%)	0.21
Lab tests	Glucose	Mean (± sd)	100.3 ± 28.1	112.1 ± 34.5	0.01
	HbA1c	Mean (± sd)	5.5 ± 0.8	5.9 ± 1.3	0.01
	CRP	Mean (± sd)	10.1 ± 7.1	13.9 ± 9.8	0.006
	Cholesterol	Mean (± sd)	182.2 ± 37.5	198.4 ± 53.1	0.008
	TG	Mean (± sd)	118.7 ± 68.8	153.8 ± 87.2	0.001
	HDL	Mean (± sd)	50.8 ± 14.8	47.7 ± 13.1	0.13
	LDL	Mean (± sd)	107.0 ± 32.8	125.5 ± 49.0	0.028
	Sodium urine	Mean (± sd)	126.2 ± 47.9	125.5 ± 49.0	0.92
	Potassium urine	Mean (± sd)	79.3 ± 34.8	76.3 ± 35.6	0.54
	GFR	Mean (± sd)	104.9 ± 22.8	95.8 ± 21.1	0.006

TABLE 5: Multiple logistic regression model for the unaware hypertensive versus the normotensive participants.

		Odds Ratio	95 % CI	P-value
Age	≤ 30	Ref	Ref	Ref
	31-40	1.09	0.25-4.65	0.91
	41-50	1.90	0.41-8.78	0.41
	51-60	3.39	0.81-14.21	0.09
	>60	7.36	1.18-33.07	0.01
Gender	Females	Ref	Ref	Ref
	Males	4.57	1.97-10.59	<0.0001
Marital Status	Married	Ref	Ref	Ref
	Single	4.55	1.16-17.76	0.02
	Others	2.27	0.68-7.54	0.17
Income Level	<600 $	Ref	Ref	Ref
	600-999.9$	0.69	0.27-1.78	0.20
	1000-2000$	0.51	0.17-1.53	0.18
	>2000$	0.26	0.06-1.15	0.07
BMI	Normal	Ref	Ref	Ref
	Overweight	2.53	0.83-7.69	0.16
	Obese	6.83	2.59-22.01	<0.0001

of the studied factors showed a significant difference at the bivariate level. After adjustment, none of the predictors was found to be statistically significant in the final model.

4. Discussion

This cross-sectional study provided an estimate of the current prevalence and control rates of HTN in a community sample representative of the GBA adult population. It highlighted the burden of the disease: 36.4% of the study participants were hypertensive, 25.3% were prehypertensive, and only 38.2% had optimal BP. The awareness rate among the hypertensive participants was estimated at 65.4% and the control rate at 61%.

Our findings of HTN prevalence is comparable to those of a cross sectional study conducted in 2013 in all six provinces of Lebanon and including a sample of 1697 participants, which reported a crude prevalence of 36.9% for HTN and 30% for pre-HTN while the control rate was 54% [7]. On the other hand, prevalence of the pre-HTN group is lower in GBA compared to the national level [7]. Both studies utilized similar methodologies, specifically the definitions of BP, which was based on BP measurements and not on self-report only. Interestingly, the control rate in GBA remained higher when compared to the national study. This can be possibly justified by the effect of urban living of our study setting. A study showed that low rates of treatment and management of HTN were obtained in the rural areas of the low to middle income countries, which was mainly due to difficulties in the accessibility to healthcare [19]. Population living in the urban settings does not encounter the same factors in terms of accessibility as those who are in rural areas, such as the costs in accessing healthcare centers, the distance to clinics, and the difference in the quality of care provided [19].

Comparing the findings of our study with similar studies in the adjacent countries, Lebanon had the higher prevalence of HTN when compared to Palestine (27.6%), Egypt (26.3%), and Turkey (31.8%) [20–22]. What ameliorates this finding is that Lebanon had better control rates of the disease compared to the rates reported from Palestine (9.5%), Egypt (8%), and Turkey (8.1%), respectively [20–22]. On the other hand, comparing the results with the West, Lebanon had higher prevalence of HTN than the developed countries such as the USA (29%) [23] and Canada (20%) [24]. Yet the control rate in Lebanon is comparable to the same countries, USA (63%) and Canada (66%) [9]. The variability across countries is multifactorial and could have occurred because of differences in the study designs and methodologies, time frames, geographic variations, lifestyle habits, and socioeconomic differences in addition to medical access and quality of care [6].

Regression analyses showed that increasing age, male gender and T2D were positive correlates for HTN. The findings were in concordance to the results of the national study by Matar et al. with similar strengths of associations [7]. In contrast to Matar et al. findings, our study identified income level as a significant correlate for HTN. The reported results showed that subjects with higher income level had lower prevalence of HTN. Our results are consistent with those reported in other studies [25, 26]. A study conducted in the United Arab Emirates demonstrated that HTN was found to be significantly higher among low income groups [25]. Another study conducted in Canada reported that income was also a negative independent correlate for HTN [26]. Therefore, several studies have found that income is a crucial socioeconomic measure to examine variables that affect the health, as it provides access to other factors such as education, medical care, goods, and services [25, 26]. A lower income level and the challenging life conditions can justify the unhealthy lifestyle habits which could influence

Table 6: The association of demographic, socioeconomic, lifestyle, anthropometric, dietary intake, and medical history and laboratory test with the uncontrolled HTN.

Variables N = 103		Controlled HTN N = 63 (61.2%)	Uncontrolled HTN N = 40 (38.8%)	P-value
Demographics				
Age	≤ 30	0(0%)	0 (0%)	0.75
	31-40	2(3.2%)	2 (5.0%)	
	41-50	12 (19.0%)	5 (12.5%)	
	51-60	25 (39.7%)	16 (40.0%)	
	≥ 60	24 (38.1%)	17 (42.5%)	
Gender	Males	14 (22.2%)	15 (37.5%)	0.09
	Females	49 (77.8%)	25 (62.5%)	
Marital status	Married	43 (68.3%)	29 (72.5%)	0.83
	Single	1 (1.6%)	1 (2.5%)	
	Others	19 (30.2%)	10 (25.0%)	
Socioeconomics				
Income	<600 $	33 (61.1%)	20 (55.6%)	0.74
	600-999.9$	15 (27.8%)	11 (30.6%)	
	1000-2000$	6 (11.1%)	4 (11.1%)	
	>2000$	0 (0.0%)	1 (2.8%)	
Education	No school /Primary	30 (61.2%)	14 (56.0%)	0.37
	Intermediate/Secondary/Technical	18 (36.7%)	10 (40.0%)	
	University degree	1 (2.0%)	1 (4.0%)	
Cigarette smoking	Never	31 (49.2%)	20 (50.0%)	0.44
	Current	22 (34.9%)	17 (42.5%)	
	Ex-smoker	10 (15.9%)	3 (7.5%)	
Narghileh smoking	Never	46 (73.0%)	32 (80.0%)	0.34
	Current	13 (20.6%)	4 (10.0%)	
	Ex-smoker	4 (6.3%)	4 (10.0%)	
Lifestyle habits				
Coffee drinking	No	6 (9.5%)	7 (17.5%)	0.36
	Yes	57 (90.5 %)	33 (82.5%)	
Alcohol drinking	Never	53 (84.1%)	27 (67.5%)	0.12
	Current	7 (11.1%)	8 (20.0%)	
	Ex-drinker	3 (4.8%)	5 (12.5%)	
Physical activity	None	9 (14.3%)	11 (27.5%)	0.13
	Yes	54 (85.7%)	29 (72.5%)	
Anthropometric measurements				
BMI (Kg/m^2)	Normal	3 (4.8%)	2 (5.0%)	0.33
	Overweight	24 (38.1%)	10 (25.0%)	
	Obese	36 (57.1%)	28 (70.0%)	
Waist circumference- abdominal obesity	No	13 (20.6%)	5 (12.5%)	0.42
	Yes	50 (79.4%)	35 (87.5%)	
Waist to hip ratio- abdominal obesity	No	7 (11.1%)	6 (15.0%)	0.76
	Yes	56 (88.9%)	34 (85.0%)	
Body fat	Mean (± sd)	34.6 ± 9.9	37.2 ± 8.4	0.27

TABLE 6: Continued.

Variables N = 103		Controlled HTN N = 63 (61.2%)	Uncontrolled HTN N = 40 (38.8%)	P-value
	Total energy -Kcal	Mean (± sd)	2795.7 ± 1439.0	2638.4 ± 1307.8	0.58
	Total protein (g/d)	Mean (± sd)	96.6 ± 57.7	87.1 ± 44.2	0.38
	Carbohydrates	Mean (± sd)	348.7 ± 188.8	336.0 ± 221.9	0.75
	Total fat	Mean (± sd)	115.9 ± 68.9	107.3 ± 61.6	0.52
Dietary intake	Saturated fat	Mean (± sd)	27.7 ± 15.5	24.7 ± 13.2	0.32
	% from carbs	Mean (± sd)	50.3 ± 9.4	50.5 ± 9.6	0.93
	% from proteins	Mean (± sd)	13.7 ± 3.0	13.7 ± 3.4	0.95
	% from fat	Mean (± sd)	36.9 ± 9.1	36.7 ± 10.4	0.89
	% from saturated fat	Mean (± sd)	8.9 ± 2.4	8.5 ± 2.5	0.42
	CAD	Cardiac catheter	14 (22.2%)	11 (27.5%)	0.54
Medical History		Previous heart attack	6 (9.5%)	6 (15.0%)	0.53
		Family history	20 (31.7%)	14 (35.0%)	0.73
	T2D		27 (42.9%)	18 (45.0%)	0.83
	Glucose	Mean (± sd)	131.5 ± 62.6	132.26 ± 62.6	0.13
	HbA1c	Mean (± sd)	6.5 ± 1.6	7.1 ± 2.0	0.13
	CRP	Mean (± sd)	14.1 ± 9.2	17.4 ± 19.0	0.24
	Cholesterol	Mean (± sd)	186.5 ± 42.3	196.1 ± 57.1	0.33
Lab tests	TG	Mean (± sd)	160.1 ± 78.2	192.4 ± 95.7	0.06
	HDL	Mean (± sd)	47.3 ± 13.0	45.3 ± 11.7	0.43
	LDL	Mean (± sd)	107.3 ± 37.0	112.4 ± 46.6	0.53
	Sodium urine	Mean (± sd)	101.7 ± 48.9	112.2 ± 39.8	0.26
	Potassium urine	Mean (± sd)	74.4 ± 31.2	76.5 ± 35.2	0.74
	GFR	Mean (± sd)	90.1 ± 26.2	83.6 ± 27.9	0.23

behaviors, leading to a higher risk of HTN [27]. Moreover, previous evidence demonstrated that socioeconomic status (SES) including the income level can shape and direct the lifestyle habits and behaviors of individuals [28]. Accordingly, maybe more effort to screen for HTN among individuals of lower income level ought to be directed.

Additionally, body fat was found to be high among the hypertensive and prehypertensive population of GBA when compared to the normal. Likewise, TG and CRP are biochemical factors that were positively associated with HTN. High TG, body fat, and CRP are factors linked to the metabolic syndrome which increases the overall cardiovascular risk [29, 30].

On the other hand, potassium was found to be the only dietary factor that is significantly negatively associated with pre-HTN. A study reported that, in borderline hypertensive patients, a low-potassium diet (16 mmol/day) for 10 days increases systolic and diastolic pressures by 7 and 6 mmHg, respectively, relative to 10 days on a high-potassium diet (96 mmol/day) [31]. Therefore, the adequate dietary intake of potassium can have an antihypertensive effect. The Dietary Approaches to Stop HTN (DASH) which relies mainly on increased consumption of fruits and vegetables, which are high in potassium, is a possible recommendation for the prehypertensive group [32]. None of the macronutrients was found to be significantly correlated to HTN and pre-HTN after the adjustment. Nevertheless, the dietary intakes from fats, carbohydrates, proteins, sodium, and total calories were found to be lower among the hypertensive when compared with the normal. These findings suggest that patients are possibly following modifications in their dietary habits for better control and management of the disease. Yet, none of the results were statistically significant.

Unaware hypertensive patients among community members not known to have HTN were mostly above the age of 60, males, single, and obese. Interestingly, the SES was no longer significant after the adjustment. Comparing the findings with those of Matar et al. (2015), results were similar showing that HTN awareness was poorer in males when compared to females and in single individuals compared to the married, yet our findings showed that unawareness was among the older subjects and those who had diabetes or hyperlipidemia [7]. Results from adjacent countries showed higher hypertension awareness is among women, older hypertensive, diabetics, obese, housekeepers, and those who have high physical activity levels [11, 33]. Similarly, male sex and older age were the main factors associated with unawareness of hypertension in a study done by Hyman and Pavlik in the United States [34].

Healthcare access and utilization play a major role in increasing the awareness of HTN. Studies showed that gender difference in the healthcare use is one of the main reasons contributing to the differences in the awareness of the disease [35–37]. Women are more likely to seek care from health practitioners, especially for gynecological services; on the other hand, heteronormative masculinity scripts dictate men to be tough and not seek help in times of need [35, 36].

We could not identify any predictor of HTN control in treated aware hypertensive patients. The control of HTN

relies on the modifications in the lifestyle habits and on pharmacologic treatment [2]. Our findings could not detect any significant association for dietary and behavioural habits. It is important to note that the dietary assessment performed in this study was based on a food frequency questionnaire, which may be limited by measurement errors, reliance on memory, and the number of food items included in the food list [38]. However, despite these potential limitations, the FFQ was shown to be the most suitable dietary assessment tool in large epidemiological studies since it assesses the subject's habitual diet over longer periods of time [39]. Other factors not studied might contribute to a poor control of HTN such as medication adherence, adequate pharmacologic treatment, psychological stress, access to healthcare, and patients' knowledge of the target BP level. A Lebanese national study that attempted to identify predictors of BP control reported that diabetes was a poor predictor for BP control, whereas the early control and the combination therapy were for better control [40]. Another national Lebanese study by Farah et al. aimed to assess the factors contributing to the control of HTN [41]. The major factors that were found to be correlated with uncontrolled BP were the low medication adherence and obesity [41]. The findings of the literature are still not enough and BP control remains a major public health challenge in Lebanon.

4.1. Limitations and Strengths. The study has several limitations. Being a cross-sectional study, general associations and hypothesis may be derived, but temporal relationship and causality cannot be established. Even though it is a community based study, selection bias is another limitation due to the small cohort of participants enrolled in the study and the female overrepresentations. The national statistics show that one-third of the Lebanese population are residing in GBA where 50.6% of the population are females while 49.4% are males [7]. The high female to male ratio in our study can be due to data collection that was done during the week days and working hours. It is possible that those who are unemployed and housewives were more likely to participate. Also, the sample was taken only from GBA which limits the generalizability of the results to the whole country. On the other hand, GBA is a major part of Lebanon where the national statistics report that 47.7% of the Lebanese population are residing in this area [7]. Therefore, the findings of this study could be considered representative for urban adults in Lebanon, which provides a ground for further epidemiologic investigations and comparison. Furthermore, variables in the study relied on biochemical and anthropometric measures rather than personal reports from subjects, hence giving us accurate and reliable data foundation to build our conclusions on.

5. Conclusion

Our findings showed that the prevalence of HTN is consistently high, yet there is an improvement in the awareness and management of the disease. The identified predictors of HTN in GBA were the same as those presented in previous studies

done in Lebanon. However, income level, body fat, and CRP were additional factors identified among HTN patients in GBA. Interestingly, among the unaware hypertensive patients who perceive themselves as normal, obesity remains a major problem in the population. Furthermore, our study could not identify any predictor for HTN control and further investigations are needed.

Our results can advise the development and establishment of national interventions by the public health sectors to achieve better awareness, primary prevention, and better control of the disease. The development of a national awareness campaign for hypertension can serve in increasing the detection of the disease, educating the community on factors impacting their BP level, and promoting the importance of following healthy lifestyle habits (healthy diet) and medication adherence.

Abbreviations

BP: Blood pressure
BMI: Body mass index
CVD: Cardiovascular diseases
CKD: Chronic kidney diseases
FBS: Fasting blood sugar
GBA: Greater Beirut Area
GFR: Glomerular filtration rate
HDL: High density lipoprotein
HbA1c: Glycosylated hemoglobin
HTN: Hypertension
JNC7:   Joint National Committee 7
JNC8:   Joint National Committee 8
Pre-HTN: Prehypertension
LDL: Low density lipoprotein
LMICs: Low and middle income countries
Mg: Milligram
Mg/dl: Milligram per deciliter
MmHg: Millimeter of mercury
OR: Odds ratio
SES: Socioeconomic status
SBP: Systolic blood pressure
TG: Triglyceride
T2D: Type 2 diabetes.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon "reasonable" request.

Conflicts of Interest

The authors have no multiplicity of interest to disclose.

Authors' Contributions

Aya Noubani and Hussain Isma'eel are equal contributors.

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Research Article

A Fortified Method to Screen and Detect Left Ventricular Hypertrophy in Asymptomatic Hypertensive Adults: A Korean Retrospective, Cross-Sectional Study

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Purpose. Left ventricular (LV) mass is determined by the wall thickness and diameter. LV hypertrophy (LVH), the increase in LV mass, is usually screened with electrocardiography but is often insensitive. We tried to fortify the rule to detect LVH using cardiothoracic ratio (CTR) in chest X-ray and well-known risk factors besides electrocardiography. *Materials and Methods.* This retrospective cross-sectional study included asymptomatic hypertensive individuals aged ≥40 y who underwent voluntary checkups including echocardiography. Independent variables to explain LVH (LV mass index>115 g/m^2 for men and >95 g/m^2 for women calculated on echocardiography) were chosen among Sokolow-Lyon voltage amplitude (SLVA), CTR and cardiovascular risk factors by multiple logistic regression analysis. The diagnostic rule to detect LVH was made by summing up the rounded-off odds ratio of each independent variable and was validated using bootstrapping method. *Results.* Among the 789 cases enrolled (202 females (25.6%), mean age 59.6±8.8 y), 168 (21.3%) had LVH. The diagnostic rule summed female, age≥65 y, BMI≥25 kg/m^2, SLVA≥35 mm, and CTR≥0.50 (scoring 1 per each). Its c-statistics was 0.700 (95% CI: 0.653, 0.747), significantly higher ($p<0.001$) than that of SLVA≥35 mm, 0.522 (95% CI: 0.472, 0.572). The sensitivity and specificity of the model were 61.9% and 72.1% for score≥2 and 30.4% and 92.9% for score≥3. The SLVA≥35 mm criteria showed sensitivity of 12.5% and specificity of 91.9%. *Conclusions.* The rule to sum up the number of the risk factors of female, age≥65 y, BMI≥25 kg/m^2, SLVA≥35 mm, and CTR≥0.50 may be a better diagnostic tool for screening LVH, than the electrocardiography-only criteria, at the score≥2.

1. Introduction

Left ventricular hypertrophy (LVH), an increase of left ventricular (LV) mass, is common in hypertensive patients and increases the risk of sudden cardiac death, cerebrovascular events, heart failure, death following myocardial infarction, and arrhythmias [1–7]. The regression of LV mass index is associated with lower incidence of cardiovascular events and improved cardiac function [8–12], and thus finding subjects at risk before clinical symptom appears is important in terms of disease prevention.

Transthoracic echocardiography is the current "gold standard" to accurately measure LV mass and confirm LVH [13–15]. Despite the advantages of echocardiography as a noninvasive imaging modality which can be performed at bedside and without radiation exposure, echocardiography is not an appropriate method for public screening tool. It is expensive, time-consuming, and expert-dependent to be used as a screening method. Instead, electrocardiography (ECG) criteria have been used as screening tools to detect LVH in asymptomatic subjects.

Enlarged cardiothoracic ratio (CTR), defined as >0.50, is another parameter to determine cardiac enlargement, which can be easily measured from chest X-ray. It is the most widely known chest radiograph index of cardiac function. Enlarged CTR, defined as >0.50, has been evaluated in patients with chronic kidney disease under hemodialysis and has shown prognostic significance [16, 17]. Both CTR and ECG can be easily obtained quickly and without use of contrast agent and potentially can be used as initial screening methods for large number of subjects [18, 19].

In current study, we evaluated diagnostic value of CTR, ECG criteria, and the well-known risk factors of LVH and tried to develop a fortified rule to screen LVH combining them, to be used in primary clinics and in real-world public population.

2. Materials and Methods

2.1. Study Subjects. The cross-sectional study was conducted retrospectively. Random samples of subjects were taken from the subjects who had healthcare check-up at Healthcare System Gangnam Center, Seoul National University Hospital. All included subjects were hypertensive patients under management or newly detected hypertensive subjects of age≥40 years, who had chest X-ray, ECG, and echocardiography within one month of the medical check-up.

Exclusion criteria were as follows: (1) missing data among any one of following: chest X-ray, ECG, or echocardiography; (2) indeterminate cardiac diameter (CD) on chest X-ray due to various reasons [20]; (3) bundle branch blocks with inappropriate S or R waves to calculate ECG-based LVH criteria [18, 19, 21]; (4) inability to calculate LV mass from echocardiography due to poor imaging window; and (5) any known significant ischemic or valvular heart disease, any type of cardiomyopathy or infiltrative disorders. From 836 subjects initially screened, 47 subjects were excluded and in final study analysis 789 hypertensive patients were included.

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital and followed the ethical guidelines of the Declaration of Helsinki as revised in 2013 (IRB No. H-1405-001-573). Due to the retrospective design using a database and medical records, informed consent was waived by the board.

2.2. Methods of Measurement, Data Collection, and Processing. Basic demographic characteristics included age, gender, height, weight, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Height and body weight were measured using a digital scale. BMI was calculated using height and weight according to the formula: BMI=weight (kg)/height (m)^2. Based on the subject-recorded questionnaires and medications, presence of comorbid conditions such as diabetes mellitus and hyperlipidemia was screened [22].

The laboratory tests were taken after fasting for at least 12 hours. Blood tests included total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting blood sugar, glycated hemoglobin, blood urea nitrogen, and serum creatinine level.
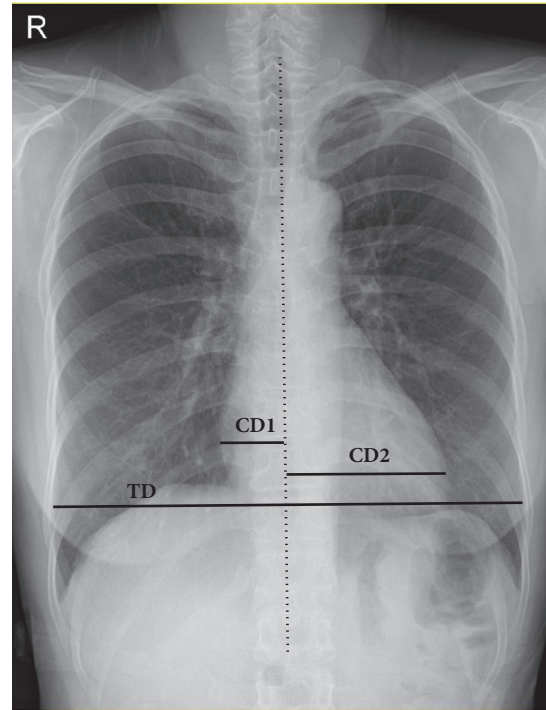

FIGURE 1: **Measurement of cardiac diameter (CD) and thoracic diameter (TD)**. On chest PA, a vertical line (dotted line) was traced parallel to the vertebral column. The greatest distances from this line to each cardiac border (CD 1 and CD 2) were summed up to get CD. TD was defined as the greatest width (TD) between the inner surfaces of ribs. CD, cardiac diameter; TD, thoracic diameter; chest PA, posteroanterior chest X-ray.

To measure CD and CTR on chest X-ray, a vertical line was traced parallel to the vertebral column and the greatest distances from the vertical line to each cardiac border were summed. Thoracic diameter (TD) was defined as the greatest width between the inner surfaces of ribs (Figure 1). CTR was calculated by CD/TD [20].

To evaluate LVH from ECG, two different criteria were used. The tallest heights of S wave in V1 and R wave in V5 or 6 were summed to render Sokolow-Lyon voltage amplitude (SLVA) [18, 19], and SLVA≥35 mm was used to define LVH [23]. With the sum of R wave in aVL and S wave in V3 set as Cornell voltage amplitude, CVA≥20 mm for women and 28mm for men were applied to define LVH by Cornell voltage criteria [24].

Echocardiographic measurement was used to calculate LV mass. LVH was defined when LV mass indexed by body surface area (BSA) was ≥115 g/m^2 for male and ≥95 g/m^2 for female subjects, respectively [13, 25]. LV mass was calculated with the linear method using echocardiography performed by experienced cardiologists:

$$\text{LV mass (g)} = 0.8 \times \left[1.04 \times \left\{ (\text{LVID} + \text{LVPWT} + \text{IVST})^3 - \text{LVID}^3 \right\} \right] + 0.6 \quad (1)$$

where LVID indicates LV internal diameter, LVPWT the LV posterior wall thickness, and IVST the interventricular septal thickness [13, 14]. LV dimensions and wall thickness were measured using M-mode. BSA (m^2) was calculated as '$\sqrt{\text{height (cm)}} \times \sqrt{\text{weight (kg)}}/60$ [26].

To minimize interrater variability, one investigator (PHE) abstracted all data of SVLA and CTR and another (NSH) verified interrater reliability by reviewing 3% of them chosen randomly.

2.3. Data Analysis. To show demographic characteristics and comorbidity, the mean and standard deviation (SD) of continuous variables and proportions of categorical values were reported. Using the t-test and chi-square test, the candidate variables to show differences between those with and without LVH were identified. The cut-off point of the *P* value was <0.20, here. Among these, continuous variables were converted into categorical ones according to spline analysis. When appropriate, well-known cut-off values were preferred.

Incorporating the chosen variables, we performed multiple logistic regression analysis by conditional forward selection to identify independent risk factors of LVH. To build an easy-to-use diagnostic rule, the authors multiplied the odds ratio (OR) of each risk factor by an arbitrary number and rounded the results to the nearest integers. The diagnostic index was defined as the sum of the corresponding simplified OR's. The discrimination accuracy to detect LVH was evaluated by calculating the area under the ROC curve and compared with that of the traditional Sokolow-Lyon criteria of LVH by the method suggested by DeLong et al. [27]. All the assumptions required for logistic regression analysis were verified.

Afterwards, this diagnostic rule was validated internally by bootstrapping method with 1,000 repetitions to show the corrected area under the curve (AUC) [28].

IBM SPSS Statistics (SPSS Inc., Chicago, IL, USA) Version 24 and R (R Foundation for Statistical Computing, Vienna, Austria [http://www.R-project.org]) with the POCR, pROC, and verification packages (http://cran.r-project.org) were used in the analyses. A two-sided $p<0.05$ was used to determine statistical significance unless described otherwise.

3. Results

The mean age of the 789 subjects was 56.9 years (SD, 8.8 years) and 202 subjects were females (25.6%). Diabetes mellitus was present in 136 subjects (17.2%) and dyslipidemia was present in 278 subjects (35.2%). LVH was detected in 168 subjects (21.3%) by echocardiography, which was more prevalent in female gender (15.0% versus (vs.) 39.6% in male vs. females, p<0.001) [29, 30]. Electrocardiographically diagnosed LVH by SLVA ≥35 mm was present in 71 subjects (9.0%), of whom 21 subjects had LVH with echocardiography diagnosis. By Cornell voltage criteria, LVH was present in 40 subjects of whom 13 subjects had LVH by echocardiography. CTR ≥0.50 was present in 157 subjects (19.9%), of whom 58 subjects had echocardiography finding of LVH. The intraclass correlation coefficients in the measurement of CD, TD, CTR, and SLVA

were 0.962, 0.993, 0.960, and 0.983, respectively (n=27, all $p<0.001$).

The study subjects were grouped into LVH group and control group according to the presence of LVH diagnosed by echocardiography. Compared to control group, LVH group had significantly greater number of female subjects, older age, higher SBP and DBP, and greater SLVA in electrocardiogram (Table 1). Among the candidate variables which showed differences ($p>0.20$ at this stage) between LVH and control groups, SBP and CTR were chosen rather than DBP and CD, respectively, considering collinearity and clinical importance. Before the logistic regression analysis, the continuous variables were categorized as age≥65 vs. <65 y, height≤1.65 m vs. >1.65 m, weight≤67 vs. >67 kg, BMI≥25 vs. <25 kg/m^2, SBP≥140 vs. <140mmHg, HDL cholesterol≥1.55 vs. <1.55mmol/L, LDL cholesterol≤2.59 vs. >2.59 mmol/L, BUN≥7.14 vs. <7.14 mmol/L, CTR≥0.5 vs. <0.5, and SLVA≥35 vs. <35mm. Since the study aim was focused on public screening, the echocardiographic variables were not taken into consideration.

After univariate logistic regression analysis, step-wise multiple logistic regression analysis was performed with these candidate variables to detect LVH. Female gender, age≥65 years, BMI≥25 kg/m^2, CTR≥0.50, and SLVA≥35 mm were chosen as the independent predictors of LVH (Table 2). Hosmer-Lemeshow goodness-of-fit was satisfied ($p=0.681$). When arbitrary number of 0.39 was multiplied to the odds ratio of each predictor and rounded up, the simplified score was 1 for each (Table 2).

The five variables described in Table 2 were used to model a new score system to detect LVH. Each variable was given one point, and higher score showed greater association with presence of LVH. The OR for LVH was 2.755 (95% CI: 1.614-4.701) for score ≥1, 4.208 (95% CI: 2.944-6.016) for score≥2, 5.716 (95% CI: 3.646-8.961) for score≥3, and 6.432 (95% CI: 2.862-14.455) for score≥4 (all $p<0.001$). No case scored 5.

The area under the ROC curve of this model was 0.700 and was internally validated by bootstrapping (95% CI: 0.655, 0.745, $p<0.001$), while that for the traditional criterion of SLVA≥35 mm was 0.522 (95% CI: 0.472, 0.572, $p=0.376$) (Figure 2). Meanwhile, those for female gender, age≥65 years, BMI≥25 kg/m^2 and CTR≥0.50 were 0.640 (95% CI: 0.590, 0.690, $p<0.001$), 0.613 (95% CI: 0.563, 0.663, $p<0.001$), 0.525 (95% CI: 0.476, 0.575, $p=0.311$), and 0.593 (95% CI: 0.542, 0.644, $p<0.001$), respectively. Thus, the areas differed significantly between the new model and the rule of SLVA≥35 mm (0.178, 95% CI: 0.130, 0.226, $p<0.001$). The sensitivity and specificity of this new model were 61.9% and 72.1% for score≥2 and 30.4% and 92.9% for score≥3. Meanwhile, the traditional SLVA≥35 mm criteria showed sensitivity of 12.5% and specificity of 91.9% (Table 3).

4. Discussion

Our study suggested a new scoring system to determine LVH more accurately, which includes clinical, radiologic, and electrical information. According to our knowledge, this is the first study to build a scoring system by combining various clinical risk factors of LVH, CTR in chest X-ray,

TABLE 1: Baseline characteristics of study subjects according to the presence or absence of echocardiographic left ventricular hypertrophy by LV mass.

	LVH (n=168)	No LVH (n=621)	p value
Demographic information			
Female, n (%)	80 (47.6%)	122 (19.6%)	<0.001**
Age, years	64 ± 10	59 ± 8	<0.001**
Diabetes mellitus, n (%)	32 (19.0%)	104 (16.7%)	0.558
Hyperlipidemia, n (%)	61 (36.3%)	217 (34.9%)	0.812
Height, m	1.63 ± 0.09	1.67 ± 0.07	<0.001**
Weight, kg	67.5 ± 11.9	70.1 ± 11.2	0.007**
BMI, kg/m^2	25.3 ± 3.1	24.9 ± 2.8	0.058
SBP, mmHg	126.4 ± 13.2	122.5 ± 13.5	0.001**
DBP, mmHg	79.7 ± 9.5	81.4 ± 9.8	0.045*
Laboratory results			
Fasting glucose, mmol/L	5.83 ± 1.00	5.88 ± 1.11	0.422
HbA1c, %	5.9 ± 0.5	5.9 ± 0.7	0.342
Total cholesterol, mmol/L	4.66 ± 0.91	4.74 ± 0.88	0.335
Triglyceride, mmol/L	1.39 ± 0.75	1.47 ± 0.87	0.295
HDL cholesterol, mmol/L	1.40 ± 0.34	1.32 ± 0.28	0.012*
LDL cholesterol, mmol/L	2.75 ± 0.75	2.90 ± 0.75	0.009**
BUN, mmol/L	6.07 ± 2.14	5.71 ± 1.78	0.063
Cr, μmol/L	79.56 ± 17.68	79.56 ± 35.36	0.359
Echocardiography measurement			
LVIDd, mm	52 ± 4	48 ± 4	<0.001**
LVIDs, mm	30 ± 4	28 ± 3	<0.001**
LVEF, %	67 ± 6	67 ± 5	0.943
IVSd, mm	11 ± 1	9 ± 1	<0.001**
LVPWd, mm	11 ± 1	9 ± 1	<0.001**
LV mass, g	213 ± 43	159 ± 33	<0.001**
LV mass/BSA, g/m^2	122 ± 18	88 ± 14	<0.001**
Radiology measurement			
CD, mm	139.4 ± 14.3	137.1 ± 14.2	0.067
CTR	0.48 ± 0.05	0.46 ± 0.04	<0.001**
Electrocardiography measurement			
SLVA, mm	25.7 ± 8.9	24.1 ± 7.2	0.042*
CVA, mm	15.5 ± 5.8	15.0 ± 5.8	0.313

BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CD, cardiac diameter; Cr, serum creatinine; CTR, cardiothoracic ratio; CVA, Cornell voltage amplitude; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IVSd, interventricular septum end-diastolic thickness; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVIDd, left ventricular end-diastolic diameter; LVIDs, left ventricular end-systolic diameter; LVPWd, left ventricular end-diastolic posterior wall thickness; LDL, low-density lipoprotein; SBP, systolic blood pressure; SLVA, Sokolow-Lyon voltage amplitude
* $p<0.05$
** $p<0.01$.

and SLVA in ECG. Although there have been studies to modify diagnostic accuracy of ECG, none had presented a scoring system including clinically significant parameters [16, 17]. With utilization of the well-known clinical risk factors, traditional ECG diagnostic criteria of LVH and CTR≥0.50, we could build a relatively clear-cut and easy-to-use model to screen LVH far better than the traditional ECG criteria [31]. Considering the sensitivity and specificity, score≥2 could be used for screening cut-off value of LVH. Meanwhile, at the score≥3, LVH could be specifically suggested (Table 3).

4.1. Screening LVH by ECG: Advantages and Limitations to Overcome.
As ECG is not costly and simple to perform, it is widely used to determine LVH in clinical practice and still remains to be the most commonly used screening tool [32, 33]. Despite the advantages, poor diagnostic accuracy and low sensitivity of ECG criteria limit its use in detecting LVH [34, 35], and there have been many studies to "adjust" ECG criteria to improve diagnostic accuracy for detection of LVH [36]. For example, Rider et al. reported obesity results in decrease of voltage amplitude and leftward shift in anatomical

TABLE 2: Logistic regression analyses to reveal the predictors of LVH by LV mass using echocardiography and the relevant simplified scores.

	OR	95% CI	p	Score* (for multivariate analysis only)
Univariate logistic regression analysis				
Female	3.718	2.590-5.339	<0.001	N/A
Age≥65 years	2.838	1.985-4.057	<0.001	N/A
Height≤1.65 m	2.807	1.980-3.978	<0.001	N/A
Weight≤67 kg	1.838	1.303-2.591	0.001	N/A
BMI≥25 kg/m^2	1.226	0.872-1.724	0.242	N/A
SBP≥140 mmHg	1.996	1.241-3.209	0.004	N/A
HDL cholesterol≥1.55 mmol/L	1.541	1.059-2.242	0.024	N/A
LDL cholesterol≤2.59 mmol/L	1.449	1.026-2.048	0.035	N/A
BUN≥7.14 mmol/L	1.618	1.061-2.469	0.025	N/A
CTR≥0.50	2.780	1.894-4.081	<0.001	N/A
SLVA≥35 mm	1.631	0.950-2.802	0.076	N/A
Multivariate logistic regression analysis to detect LVH				
Female	3.544	2.370-5.299	<0.001	1
Age≥65 years	2.205	1.500-3.241	<0.001	1
BMI≥25 kg/m^2	1.591	1.084-2.337	0.018	1
CTR≥0.50	1.774	1.163-2.707	0.008	1
SLVA≥35 mm	2.205	1.231-3.950	0.008	1

BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CTR, cardiothoracic ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; N/A, not applicable; OR, odds ratio; SBP, systolic blood pressure; SLVA, Sokolow-Lyon voltage amplitude.
*To build an easy-to-use screening rule to detect LVH, the score was rendered by multiplying the OR by an arbitrary number of 0.39 and rounding it up.

TABLE 3: Diagnostic accuracy of the new model to detect left ventricular hypertrophy by echocardiography according to the scores of the new system.

Score*	Sensitivity	Specificity	LR (+)	LR (-)
≥1	89.9%	23.7%	1.18	0.43
≥2	61.9%	72.1%	2.22	0.53
≥3	30.4%	92.9%	4.28	0.75
≥4	9.5%	98.4%	5.94	0.92

BMI, body mass index; CTR, cardiothoracic ratio; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio; SLVA, Sokolow-Lyon voltage amplitude.
*Age≥65 y, female, BMI≥25 kg/m^2, SLVA≥35 mm, and CTR≥0.50 were scored 1 for each.

axis, thereby causing even poorer sensitivity and diagnostic accuracy of ECG [36].

4.2. Screening LVH by Chest X-Ray: Use of CTR. Chest X-ray is another commonly used diagnostic tool. The cardiac silhouette is often evaluated to determine whether there is chamber enlargement, and CTR of 50% from chest X-ray has been considered as a cut-off value reflecting LV enlargement [37]. From a pooled analysis including 466 patients, CTR alone had 83.3% sensitivity, 45.4% specificity, 43.5% positive predictive value, and 82.7% negative predictive value [17], making CTR neither valuable as a screening nor a confirmatory test. There also has been a study showing increase of CTR by 2.0% over 9 years of follow-up, although clinical significance had been questioned [38]. Increase of CTR in elderly is due to not only increase in cardiac size but also decrease in thoracic diameter, which is associated with aging. Moreover, CTR has also failed to show strong predictive value or correlation with LV dysfunction [39, 40].

4.3. Screening LVH by Echocardiography and Cardiovascular Magnetic Resonance (CMR): Advantages and Limitations to Overcome. Imaging modalities such as transthoracic echocardiography [41] and CMR are accurate determinants of LVH, and their accuracy exceeds that of ECG. However, such imaging modalities are not always available, are difficult to operate, and are also expensive, which limit the wide use as public screening tools. Rather, these imaging modalities can give definite diagnosis and quantitative measurements.

4.4. Study Limitation. Since our study subjects include a narrow spectrum of asymptomatic hypertensive patients, it should not be extrapolated to general population before further evaluation. The new scoring system we proposed here needs further validation in mass population, and the diagnostic performance should be compared to that of classical modalities. The new scoring system as a prognosticator should also be evaluated, since this study did not evaluate prognosis and outcome. Nevertheless, given poor diagnostic
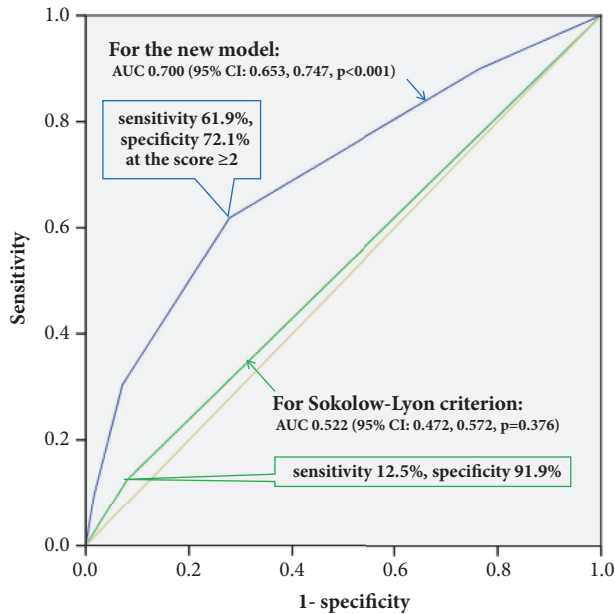
FIGURE 2: **The receiver operating characteristic curves of the new model and the traditional Sokolow-Lyon criterion to detect left ventricular hypertrophy (LVH).** The new model is the sum of the number of following risk factors: age≥65 y, female, BMI≥25 kg/m^2, SLVA≥35 mm, and CTR≥0.50. The Sokolow-Lyon criterion is positive when the Sokolow-Lyon voltage amplitude is ≥35 mm. AUC, area under curve; CI, confidence interval.

value of ECG as a single parameter to determine LVH and poor accessibility to imaging modality for public screening method, our new scoring system allows simple and readily available assessment to determine LVH.

To conclude, the new scoring system from our study allows simple and readily available assessment to determine LVH. This simple scoring system significantly improved the power of ECG or CTR to detect LVH. Improving diagnostic accuracy allows early detection of LVH, which eventually will help reducing end-organ damage and other complications related to LVH, especially in the perspective of primary care and public health. Although not studied yet, it may eventually help reduce adverse events associated with LVH.

Data Availability

The original raw data used to support the findings of this study are restricted by the Institutional Review Board of Seoul National University Hospital and Healthcare Research Institute, Gangnam Center, in order to protect patient privacy. Data are available from the corresponding author (Sang-Hoon Na, nasanghoon@gmail.com) for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

None of the authors have any financial relationships with any company or any other bias or conflicts of interest.

Authors' Contributions

Hyo Eun Park (orcid.org/0000-0001-7233-1771) determined the study design, collected the data, performed the statistical analysis, and drafted the manuscript. Sung-Bin Chon (orcid.org/0000-0001-8783-3117) conceived the idea, determined the study design, performed the statistical analysis, and drafted the manuscript. Sang Hoon Na (orcid.org/0000-0002-1289-7965) conceived the idea, determined the study design, collected the data, and revised the manuscript. Heesun Lee (orcid.org/0000-0003-4037-3955) collected the data and revised the manuscript. Su-Yeon Choi (orcid.org/0000-0001-9977-4740) collected the data and revised the manuscript. All the authors have read and approved the final draft of the manuscript. Hyo Eun Park and Sung-Bin Chon have equally contributed to this study. Hyo Eun Park and Sung-Bin Chon have both contributed as co-first authors to this manuscript.

Acknowledgments

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Research Article

Hypertension Is an Independent Predictor of Multivessel Coronary Artery Disease in Young Adults with Acute Coronary Syndrome

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Background. Risk factors of multivessel coronary artery disease (CAD) among young acute coronary syndrome (ACS) patients remain elusive now. *Methods*. This retrospective study analyzed data from 187 consecutive young (age ≤45 years) ACS patients (75 STEMI, 30 NSTEMI, and 72 unstable angina) hospitalized in our hospital from January 2012 to December 2016. Thirty-six young male patients with normal coronary angiography (CAG) findings (no-CAD), who underwent CAG due to suspected chest pain in this period, served as control group. There were 83 patients with single-vessel disease (SVD) and 104 patients with multiple-vessel disease (MVD) among ACS patients. Patients were followed up for a mean of 267±124 days by clinical visit or telephone calls. *Results*. All included patients were male. Prevalence of hypertension (57.2% vs. 30.6%, p=0.002) and smoking (70.6% vs. 52.8%, p=0.049) was significantly higher in ACS patients than in no-CAD patients. Prevalence of hypertension (72.1% vs. 38.6%, p<0.001) and body mass index (BMI) were significantly higher in MVD group than in SVD group. Multivariable analysis revealed that hypertension was an independent risk factor for MVD after adjustment for age, gender, BMI, smoking, family history of premature CAD, hyperlipidemia, left ventricular ejection fraction, and brain natriuretic peptide (odds ratio=3.71, 95% confidence interval=1.84-7.46, p<0.001). Rate of major adverse cardiovascular events (MACE) during follow-up (20.2% vs. 4.8%) was significantly higher in MVD group compared with SVD group. *Conclusions*. Hypertension is an independent predictor of MVD and MVD is associated with increased MACE rate compared to SVD in young ACS patients during the short-term follow-up.

1. Introduction

Risk factor profiles, clinical presentations, and prognosis might differ between young patients with acute coronary syndrome (ACS) and elderly ACS patients [1–4]. Previous studies showed that the prevalence of ACS among population less than 45 years of age (young ACS) ranged from 2% to 10% [4–6]. Young ACS cases were more prevalent among the Malays (49.8%), followed by Indians (24.4%), Chinese (21.8%), and other races (4.1%) [2]. Risk factors of ACS are age-dependent. Jamil et al. reported that prevalence of smoking (79.2% vs. 66.2%, p<0.001) was significantly higher, while prevalence of diabetes (12.1% vs. 25.6%, p<0.001), hypertension (34.4% vs. 57.4%, p<0.001), and hyperlipidemia (39.7% vs. 50.1%, p<0.001) was significantly lower in young ACS patients compared to elderly (>55 years old) ACS

patients [7]. Smoking was identified as one of the major risk factors of ACS in young adults [2].

Several randomized controlled trials hinted that multivessel coronary artery disease (CAD) may occur in up to 50% of all CAD patients [8, 9]. Previous studies also demonstrated that patients with multiple-vessel disease (MVD) faced substantially increased risks of mortality and major adverse cardiac events, such as reinfarction or need for urgent revascularization after successful primary percutaneous coronary intervention (PCI) [10, 11]. It is known that incidence of diabetes, advanced age, impaired left ventricular function, and history of stroke are usually high in MVD patients [12, 13].

At present, there are only scanty reports on the prevalence and risk factors as well as outcome of MVD in young ACS patients. In the present study, we compared the risk factors

and short-term outcome between young ACS patients with single-vessel disease (SVD) or MVD.

2. Methods

2.1. Study Population. In total, 187 consecutive young male adult (aged ≤45 years) ACS patients hospitalized in our department between January 2012 and December 2016 were enrolled in this study. Thirty-six young male patients with normal coronary angiography (CAG) findings (no-CAD), who underwent CAG due to suspected chest pain in this period, served as control group. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Written informed consent was obtained from all patients.

ACS refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). UA was defined as angina pectoris or equivalent ischemic discomfort with at least one of three features: (1) it occurs at rest (or with minimal exertion), usually lasting >10 minutes; (2) it is severe and of new onset (i.e., within the prior 4-6 weeks); (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previously) [14]. STEMI was defined as the presence of typical chest pain accompanying symptoms for a duration of at least 30 minutes but <12 hours in the presence of ST-segment elevation ≥1 mm in at least 2 contiguous leads, or new or undetermined duration of left bundle branch block in association with elevated cardiac enzymes [creatine kinase myocardial band (CK-MB) and Troponin I] [15]. NSTEMI was defined as ECG ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or angina equivalent) [15]. SVD referred single-vessel lumen stenosis ≥50%, luminal stenosis of left main coronary artery greater than 50%; MVD referred at least two main arteries with stenosis of vessel lumen ≥50%, luminal stenosis of left main coronary artery >50% by CAG [16, 17]. The degree of coronary artery stenosis was visually rated by 2 experienced interventional cardiologists. Hypertension was defined as a history of systolic blood pressure (SBP) ≥140mmHg or a diastolic blood pressure (DBP) ≥90mmHg or documented hypertension on at least two occasions in outpatient clinics or known hypertension under antihypertensive medication regardless of the current blood pressure [18]. Smoking was classified into three categories: never smokers, ex-smokers (those who had smoked regularly but had stopped smoking at least six months before the survey), and current smokers. We used the 2016 American Diabetes Association (ADA) guidelines for the diagnosis of diabetes [19], and the 2013 ACC/AHA guidelines management of dyslipidemias for the diagnosis of hyperlipidemia [20].

Procedural factors recorded included the infarct-related artery, number of diseased vessels, number of stents, and thrombus aspiration (TA) device use. Apart from the patient's baseline characteristics (ECG recordings, age, sex, hypertension, smoking status, hyperlipidemia, and family history of premature CAD and history of previous ACS), the following biochemical indices were analyzed: CK-MB, complete lipid profile, blood cell count, urea, creatinine, brain natriuretic peptide (BNP), and hepatic aminotransferases. Echocardiography was performed in all patients after CAG and/or PCI. All patients were followed up and treated according to the current guidelines of ACS [21].

2.2. Outcomes. The primary clinical outcome was major adverse cardiac events (MACE), defined as all-cause mortality, recurrent MI, stroke, coronary artery bypass graft (CABG), and repeat PCI during the follow-up period. Secondary clinical outcomes included in-hospital and 30 days all-cause mortality rate. The follow-up was made by clinical visit or telephone calls.

2.3. Statistical Analysis. Continuous variables are expressed as mean ± SD and categorical variables as number (percent). The data were analyzed by homogeneity of variances test. Continuous data with normal distribution were assessed by Student's t-test or one-way ANOVA with post hoc test (Bonferroni) as indicated. Nonnormal distribution data were tested by two-tailed Mann–Whitney U test or Kruskal-Wallis nonparametric test as indicated. Categorical data were compared across groups using Chi-square test or Fisher's exact test as appropriate. The associations of hypertension with MVD were evaluated using univariate and multivariate binary logistic regression models. Odds ratio (OR) and 95% confidence interval (CI) for MVD were calculated. In the multivariate models, age, gender, body mass index (BMI), hyperlipidemia, smoking, and family history of premature coronary artery disease, albumin, BNP, and left ventricular ejection fraction (LVEF) were included as covariates. P value <0.05 (two-tailed test) was considered statistically significant. The statistical analysis was performed using the SPSS statistical software, version 23.0 (IBM SPSS Statistics, Chicago, USA).

3. Results

3.1. Patient Characteristics. Table 1 shows the patient characteristics. All subjects are male. The median age of the MVD group was significantly older than that of control group (p=0.024). Hypertension was diagnosed in 118 out of 233 subjects (53%). Forty-four hypertensive patients received antihypertensive medication and the rest received no antihypertensive medication, and blood pressure was controlled in 19 out of 44 (43.2%) treated hypertensive patients. Hypertension and smoking were more frequent in the ACS group compared with no-CAD group (57.2% vs. 30.6%, p=0.002, and 70.6% vs. 52.8%, p=0.049, respectively). Regional wall motion abnormality was present in 50.8% of ACS patients. The prevalence of hypertension was significantly higher in MVD group than in SVD group (72.1% vs. 38.6%, p<0.001).

Table 2 presents the laboratory findings. WBC count, CK-MB, myoglobin, and high-sensitivity troponin I levels were significantly higher in ACS group than in no-CAD group and were similar between SVD and MVD groups. Prevalence

TABLE 1: Clinical characteristics.

	No-CAD	ACS	
		SVD	MVD
	N=36	N=83	N=104
Age (years)	41 (37-43)	40 (38-44)	42 (40-45)∗
Gender (M/F)	36/0	83/0	104/0
BMI (kg/m^2)	26.8±4.8	26.2±3.5	27.8±3.6†
Baseline SBP (mmHg)	131.5±14.2	127.0±20.1	128.6±19.4
Baseline DBP (mmHg)	81.6±9.0	78.9±13.5	80.3±15.1
HR (beats/min)	70.6±15.4	70.7±12.9	72.0±14.4
Hypertension [n (%)]	11 (30.6)	32 (38.6)	75 (72.1)∗†
Duration (years)	5.7±3.8	4.8±4.5	6.9±5.4
Family history [n (%)]	6 (16.9)	11 (13.3)	21 (20.2)
Smoking [n (%)]	19 (52.8)	64 (77.1)∗	68 (65.4)∗
Duration (year)	16.5±7.9	17.9±6.6	18.9±7.9
Consumption (cigarettes/day)	19.7±12.7	22.3±10.5	24.9±13.3
Alcohol use [n (%)]	6 (16.7)	14 (16.9)	13 (12.5)
Duration (year)	12.5 (10-20)	20 (17.5-20)	20 (10-20)
Consumption (g/day)	64 (20-103)	75 (27-150)	20 (20-75)
Family history of premature CAD [n (%)]	5 (13.9)	15 (18.1)	29 (27.9)
Diabetes mellitus [n (%)]	0	0	0
Hyperlipidemia [n (%)]	0	3 (3.6)	3 (2.9)
Echocardiography			
LVEF (%)	62.6±2.7	59.7±6.7	58.2±6.4∗
Regional wall motion abnormality [n (%)]	0	41 (49.4)∗	53 (52.0)∗

∗p<0.05 vs. no-CAD group; †p<0.05 vs. SVD group. ACS: acute coronary syndrome; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; MVD: multivessel coronary artery disease; SBP: systolic blood pressure; SVD: single-vessel disease.

of hyperlipidemia was low in this cohort (0% in no-CAD group and 3.2% in ACS group (p>0.05). Red blood cell count, platelet count, BNP, total cholesterol, triglyceride, low-density lipoprotein cholesterol, glucose, blood urea nitrogen, and uric acid level were similar among the three groups (Table 2).

3.2. Procedural and Coronary Artery Involvement Characteristics. Angiographic and procedural characteristics of the study population were listed in Table 3. The prevalences of left anterior descending artery (LAD), circumflex artery (LCX), and right coronary artery (RCA) lesion in the MVD group were significantly higher than in the SVD group. As shown in Figure 1, hypertension is related to higher prevalence of LAD, LCX, and RCA lesion. Additionally, prevalence of LAD-related stenosis (75.4%) was significantly more common than that of RCA (63.6%) and LCX-related stenosis (44.9%) in patients with hypertension (both p<0.001, Figure 1).

3.3. Hypertension and Smoking Are Independent Risk Factors for ACS in Young Adults. Table 4 shows the binary logistic regression results for ACS. Hypertension served as an independent risk factor for ACS (unadjusted OR 3.16, 95% CI 1.48-6.78, p=0.003), after adjustment for age, gender, and BMI (OR 2.91, 95% CI 1.30-6.52, p=0.009) and after adjustment for age, gender, BMI, smoking, family history of premature coronary artery disease, and hyperlipidemia
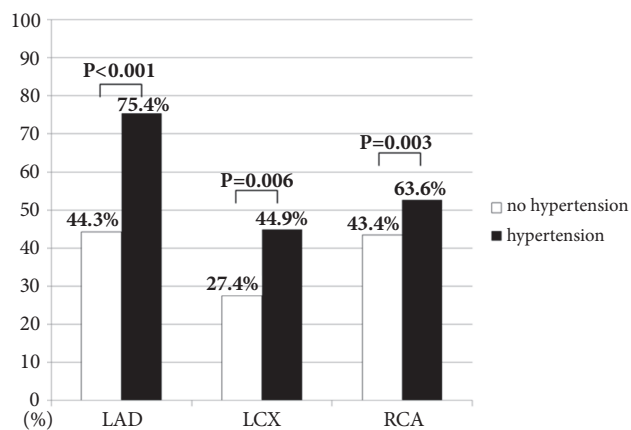

FIGURE 1: **The prevalence of involved vessels in the patients with or without hypertension**. Note that the prevalences of LAD-, RCA-, and LCX-related stenosis in patients with hypertension were higher than those in patients without hypertension. Additionally, in patients with hypertension, the LAD-related stenosis was more common compared with RCA- and LCX-related stenosis, p<0.001. LAD: left anterior descending artery; LCX: circumflex artery; RCA: right coronary artery.

(OR 3.42, 95% CI 1.48-7.88, p<0.001). Smoking is also an independent risk factor for ACS (unadjusted OR 2.04, 95% CI 0.99-4.19, p=0.052), after adjustment for age, gender,

TABLE 2: Laboratory findings.

	No-CAD	ACS	
		SVD	MVD
	N=36	N=83	N=104
WBC count (10^9/L)	6.2 (5.3-7.5)	11.7 (6.8-14.6)∗	12.3 (6.6-14.6)∗
Hemoglobin (g/L)	151.5±11.4	149.4±13.9	153.2±16.5
Platelet count (10^9/L)	209.7±56.7	217.9±45.6	221.5±50.7
CK-MB (ng/mL)	1.12 (0.9-2.7)	30 (2.3-52.0)∗	31 (2.4-56.0)∗
Myoglobin (ng/mL)	34.0 (23.5-53.0)	439.7 (35.0-500)∗	426.5 (35.3-558.2)∗
High-sensitivity troponin I (ng/mL)	0.08 (0.05-0.29)	5.2 (0.1-6.8)∗	5.2 (0.3-8.6)∗
BNP (pg/ml)	17.3 (8.7-40.6)	40 (17.3-82.3)∗	60 (26.2-127.5)∗
Total protein (g/L)	68.2±6.4	63.0±7.8∗	62.9±6.6∗
Albumin (g/L)	42.4±4.1	39.2±5.1∗	39.2±4.5∗
Globulin (g/L)	24.7±4.5	25.6±3.8	25.6±3.7
A/G	1.7±0.3	1.8±2.7	1.6±0.4
TG (mmol/L)	1.3 (0.9-1.8)	1.5 (1.2-2.0)	2.5 (1.4-2.5)∗
TC (mmol/L)	4.4±1.2	4.5±1.3	4.7±1.3
HDL-C (mmol/L)	1.2±0.3	1.1±0.3	1.1±0.2
LDL-C (mmol/L)	2.4±1.0	2.8±1.0	2.8±1.0
GLU (mmol/L)	5.1±0.8	5.4±1.4	5.5±1.2
BUN (mmol/L)	5.3±1.0	5.1±1.3	5.1±1.4
SCr (μmol/L)	89.2±14.1	87.5±17.2	90.7±15.5
Uric Acid (μmol/L)	331.8±127.5	349.6±115.9	370.9±93.6

∗$p<0.05$ vs. no-CAD group, †$p<0.05$ vs. SVD group. ACS: acute coronary syndrome; A/G: albumin to globulin ratio; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; CAD: coronary artery disease; CK-MB: creatine kinase myocardial band; GLU: glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MVD: multivessel coronary artery disease; RBC: read blood cell; SCr: serum creatinine; SVD: single vessel disease; TC: total cholesterol; TG: triglyceride; WBC: white blood cell.

TABLE 3: Angiographic and procedural characteristics.

	No-CAD	ACS	
		SVD	MVD
	N=36	N=83	N=104
Stenosis-related artery LM [n (%)]	0	1 (1.2)	3 (2.9)
Stenosis-related artery LAD [n (%)]	0	40 (48.2)∗	96 (92.3)∗†
Stenosis-related artery LCX [n (%)]	0	11 (13.3)∗	71 (68.9)∗†
Stenosis-related artery RCA [n (%)]	0	31 (37.3)∗	90 (86.5)∗†
TA device used [n (%)]	0	6 (7.2)	7 (6.7)
Number of stents	0	0.8±0.7∗	1.1±0.9∗†
Prior MI [n (%)]	0	0	0
Prior PCI [n (%)]	0	0	0
Prior CABG [n (%)]	0	0	0

∗$p<0.05$ vs. no-CAD group, †$p<0.05$ vs. SVD group. ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CAD: coronary artery disease; LAD: left anterior descending artery; LCX: circumflex artery; LML left main; MIL myocardial infarction; MVD: multivessel coronary artery disease; PCI: percutaneous coronary intervention; RCA: right coronary artery; SVD: single-vessel disease; TA: thrombus aspiration.

and BMI (OR 2.36, 95% CI 1.12-4.96, p=0.024) and after adjustment for age, gender, BMI, hypertension, family history of premature coronary artery disease, and hyperlipidemia (OR 2.49, 95% CI 1.16-5.34, p=0.019). BNP and LVEF were associated with the prognosis of ACS patients. After adding these two indexes as adjusted cofounders, the predicting efficacy of hypertension and smoking weakened to the borderline significant level: hypertension (p=0.077) and smoking (p=0.071).

3.4. Hypertension Is an Independent Risk Factor for MVD in Young ACS Patients. Table 5 shows the binary logistic regression results for MVD. Hypertension remained as an independent risk factor for MVD (unadjusted OR 4.20, 95% CI 2.27-7.77, p<0.001) after adjustment for age, gender, and BMI (OR 3.59, 95% CI 1.89-6.83, p<0.001); after adjustment for age, gender, BMI, smoking, family history of premature coronary artery disease and hyperlipidemia (OR 3.63, 95% CI 1.88-7.01, p<0.001); after adjustment for age, gender, BMI,

Table 4: Hypertension and smoking for prediction of acute coronary syndrome based on multivariable logistic regression models (n=223).

	Unadjusted OR	95% CI	p value
Hypertension	3.16	1.48–6.78	0.003
Smoking	2.04	0.99–4.19	0.052
	Adjusted OR	95% CI	p value
Hypertension (Adjusted for age, gender, and BMI)	2.91	1.30–6.52	0.009
Hypertension (Adjusted for age, gender, BMI, hyperlipidemia, smoking, and family history of premature CAD)	3.42	1.48–7.88	<0.001
Hypertension (Adjusted for age, gender, BMI, hyperlipidemia, smoking, family history of premature CAD, BNP, and LVEF)	2.94	0.89–9.73	0.077
Smoking (Adjusted for age, gender, and BMI)	2.36	1.12–4.96	0.024
Smoking (Adjusted for age, gender, BMI, hyperlipidemia, hypertension, and family history of premature CAD)	2.49	1.16–5.34	0.019
Smoking (Adjusted for age, gender, BMI, hyperlipidemia, hypertension, family history of premature CAD, BNP, and LVEF)	2.72	0.92–8.07	0.071

BMI: body mass index; BNP: brain natriuretic peptide; CAD: coronary artery disease; CI: confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio.

TABLE 5: Hypertension for prediction of multivessel coronary artery disease based on multivariable logistic regression models (n=187).

	Unadjusted OR	95% CI	p value
Hypertension	4.20	2.27-7.77	<0.001
	Adjusted OR	95% CI	p value
Hypertension (Adjusted for age, gender, and BMI)	3.59	1.89-6.83	<0.001
Hypertension (Adjusted for age, gender, BMI, hyperlipidemia, smoking, and family history of premature CAD)	3.63	1.88-7.01	<0.001
Hypertension (Adjusted for age, gender, BMI, albumin, BNP, and LVEF)	3.71	1.84-7.46	<0.001

BMI: body mass index; BNP: brain natriuretic peptide; CAD: coronary artery disease; CI: confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio.
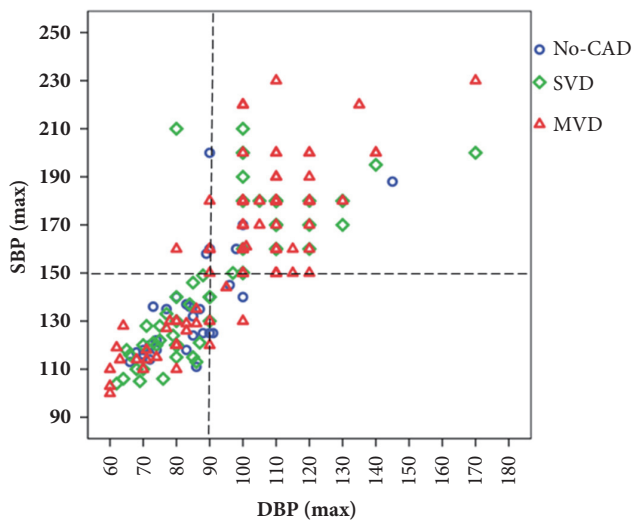

FIGURE 2: **Scatter plot of SBP and DBP among patients with no-CAD, SVD, and MVD**. Note that incidence of hypertension [SBP > 150mmHg (y-axis) and/or DBP > 90mmHg (x-axis)] was significantly higher in MVD patients (75 out of 104, 72.1%) than in patients with SVD (34 out of 83, 40.5%) and in no-CAD patients (16 out of 37, 44.4%). DBP: diastolic blood pressure; MVD: multivessel coronary artery disease, no-CAD: no coronary artery disease; SBP: systolic blood pressure; SVD: single-vessel disease.

BNP, and albumin (OR 3.96, 95% CI 1.96-7.99, p<0.001); and after adjustment for age, gender, BMI, albumin, BNP, and LVEF (OR 3.71, 95% CI 1.84-7.46, p<0.001). As shown in Figure 2, incidence of hypertension [SBP >150mmHg and/or DBP >90mmHg] was 72.1% in MVD group, 40.5% in SVD group, and 44.4% in no-CAD group (p<0.001). Patients with SBP >150mmHg and/or DBP >90mmHg were significantly associated with MVD in this cohort (sensitivity 72% and specificity 58%).

3.5. In-Hospital and 30-Day Clinical Outcome. In-hospital MACE rates were 0.0% in the SVD and MVD groups; the 30-day MACE rate was 0.0% in SVD group and 1% (n=1, death) in MVD group (p=0.37).

3.6. Short-Term Clinical Outcome. The mean follow-up time was 267±124 days. MACE rate was significantly higher in

MVD group (20.2%, 18 repeat PCI and 3 CABG) compared with SVD group (4.8%, 4 repeat PCI, p=0.002). There was no death during the follow-up period in this patient cohort. There was no significant difference between SVD and MVD groups in the rates of recurrent MI [1.2% (n=1) vs. 1.9% (n=2), p=0.698], stroke (0.0% vs. 0.0%), and CABG [0.0% (n=0) vs. 2.9% (n=3), p=0.119] during the follow-up period.

4. Discussion

To the best of our knowledge, this is the first study to evaluate the association between hypertension and MVD in young ACS patients. The major findings of the present study are as follows: Firstly, the presence of hypertension, but not smoking, is an independent predictor of MVD in young patients with ACS. Secondly, the rate of MACE was significantly higher in MVD group compared with SVD group during the 267±124 days of follow-up. Our results thus highlight the role of hypertension in the pathogenesis of MVD in young ACS patients, suggesting that hypertension control serves as an important strategy for the prevention and treatment of MVD in young ACS patients.

4.1. Risk Factors of ACS in Young Adults. Previous investigations have reported that young ACS patients have a different risk factor profile compared with elderly ACS patients [7, 22–24]. Hypertension is a known important risk factor for the development of coronary artery disease [25]. The impact of smoking on elderly patients with coronary artery disease is well established, while conflicting results existed on the impact of smoking in young adults with coronary artery disease [25, 26]. It was reported that the prevalence of hypertension was 25% in young coronary artery disease patients as compared to 13% in young non-coronary artery disease subjects and the prevalence of hypertension was much higher in elderly individuals with coronary artery disease than in young coronary artery disease patients [27]. In this study, we showed that prevalence of hypertension in young ACS patients was higher than previously reported and hypertension was more frequent in the ACS group compared with the no-CAD group (57.2% vs. 30.6%, p=0.002) and hypertension, together with smoking, served as independent risk factors for ACS. Conflicting results were reported on the impact of diabetes in young ACS patients [25, 26]. There is

no diabetic patients in our real-world-derived patient cohort, there was also no young female ACS patients in our cohort, and the contribution of diabetes and gender effect could thus not be evaluated based on our data. Our study found that hypertension and smoking are the major risk factors of young male ACS patients, while hyperlipidemia and family history of coronary artery disease played only a negligible role in young male ACS patients based on data from this patient cohort.

4.2. Association between Hypertension and MVD in Young ACS Patients. The association between hypertension and MVD in young ACS patients remains controversial. Sukhija et al. observed higher prevalence of MVD in hypertensive patients compared to nonhypertensives [27]. However, Zand Parsa et al. did not find any relationship between hypertension and MVD [28]. Our results indicated a strong association between hypertension and MVD in young male ACS patients, in that the prevalence of hypertension is as high as 72.1% in MVD group compared to 38.6% in SVD group (p<0.001, Figure 2). Moreover, results of the ordinal logistic regression model for MVD revealed that hypertension was a significant independent risk factor for MVD after adjustment for smoking, BMI, family history of premature CAD, BNP, LVEF, and hyperlipidemia in young male ACS patients. In addition, our results suggested that SBP >150mmHg and/or DBP >90mmHg as the cut-off value could fairly predict the presence of MVD (sensitivity of 72% and specificity of 58%) in young male ACS patients.

4.3. Smoking and Prevalence of ACS and MVD in Young Adults. Previous studies have demonstrated that smoking is the most important risk factor associated with the severity of coronary artery disease and is significantly linked with increased risk of coronary plaque vulnerability, myocardial infarction, and cardiovascular death [29, 30]. Previous report showed that the prevalence of smoking in younger coronary artery disease individuals (<45 years of age) ranged from 60% to 90% as compared to 24% to 56% in subjects aged 45 years and over [31, 32]. In addition, smoking served as the most important modifiable risk factor for young adult patients with ACS [24]. Our data are in accordance with previous findings in that the prevalence of smoking was high (70.6%) in young ACS patients and smoking was an independent predictor of ACS in young adults [OR: 2.49 (95% CI 1.16-5.34)] after adjustment for age, gender, BMI, hyperlipidemia, hypertension, and family history of premature CAD (Table 4). However, smoking was not an independent risk factor after adding BNP and LVEF as adjusted cofounders for ACS, and smoking was not an independent risk factor for MVD.

4.4. Outcome of Young MVD Patients. Previous studies demonstrated that MVD was associated with worse prognosis compared to SVD patients [10, 33]. In this study, the in-hospital and 30-days MACE rates were similarly low in SVD group and MVD group (in-hospital MACE rate was both 0.0% in SVD and MVD groups and the 30-day MACE rate was 0.0% in SVD group and 1% in MVD group). During the short-term follow-up, there was no record on recurrent MI and stroke in young ACS patients. As expected, the rate of MACE rate was significantly higher in MVD group (20.2%, 18 repeat PCI and 3 CABG) than in SVD group (4.8%, 4 repeat PCI, p=0.002). It is to note that the relatively low in-hospital and 30-day MACE rate as well as the low MACE rate during the short-term follow-up period from patients in this cohort might be partly due to the use of new-generation drug-eluting stents. Recent studies suggested that stent thrombosis is less frequent with newer drug-eluting stents as compared to bare metal stents [34–36].

5. Limitations

The current study has several limitations. First, it was a retrospective and nonrandomized single-center study and caution is thus needed to extrapolate present study results to general young ACS and MVD population. Second, the relatively small patient cohort number serves as another study limitation. Third, there was no young female ACS patient in this cohort; this might relate to lower prevalence of ACS in young female population in our region; there is also no diabetic patient in our patient cohort. Therefore, our results could not be used to evaluate the contributing impact of diabetes and female gender on the pathogenesis of ACS and coronary vessel lesion, as well as outcome in young adults. Nevertheless, our patients are consecutive homogeneous unselected young patients with ACS; therefore, our data might exactly mirror the real-world scenario of young ACS as well as MVD patients in our region.

6. Conclusions

Hypertension serves as an independent risk factor of MVD and related to higher MACE rate during the short-term follow-up (death, repeat PCI, and CABG) in young male adults with ACS. Our results thus highlight the role of hypertension in the pathogenesis of MVD in young male ACS patients, indicating that rigorous hypertension control might be an important strategy for the prevention and treatment of MVD in young male ACS patients.

Data Availability

The data used to support the findings of this study are included within the article. The other data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors report no conflicts of interest.

Authors' Contributions

Junhua Ge and Jian Li contributed equally to this work.

Acknowledgments

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Research Article

Value of Assessing Autonomic Nervous Function by Heart Rate Variability and Heart Rate Turbulence in Hypertensive Patients

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Purpose. To explore the relationship between blood pressure control and autonomic nervous function assessing by heart rate variability (HRV) and heart rate turbulence (HRT) in hypertensive patients. *Methods*. A total of 120 consecutive hypertensive patients and 80 nonhypertensive patients (N-HP group) were enrolled in this study. The hypertensive patients were divided into controlled blood pressure and uncontrolled blood pressure groups according to their blood pressure on admission. All subjects underwent 24-hour Holter monitoring. This study compared HRV and HRT in nonhypertensive and hypertensive patients and hypertensive patients with controlled and uncontrolled blood pressure. HRV parameters include square root of mean of the sum of squares of successive NN interval differences (rMSSD), number of successive NN intervals differing by > 50ms divided by the total number of successive NN intervals (pNN50), very low frequency (VLF) at frequency between 0.0033 and 0.04 Hz, low frequency (LF) at frequency between 0.04 and 0.15 Hz, and high frequency (HF) at frequency between 0.15 and 0.4 Hz. Turbulence slope (TS) belongs to HRT parameters. *Results*. TS, rMSSD, pNN50, VLF, LF, and HF values were significantly lower in the HP group than in the N-HP group. Multiple logistic regression analysis showed that reduced TS, rMSSD, pNN50, LF, and HF values were risk factors of hypertension. TS, rMSSD, pNN50, VLF, LF, and HF values were significantly lower in hypertensive patients with uncontrolled blood pressure than in hypertensive patients with controlled blood pressure. Multiple logistic regression analysis showed that reduced TS, rMSSD, pNN50, VLF, LF, and HF values were risk factors for uncontrolled blood pressure. *Conclusions*. This study indicates impaired autonomic nervous function in hypertensive patients, especially in hypertensive patients with uncontrolled blood pressure despite guideline recommended antihypertensive medications.

1. Introduction

Hypertension is a major disease that damages people's health. Long-term hypertension could impair major organs such as heart, brain, kidneys, and blood vessels, which is related to considerable mortality [1]. Sympathetic overactivation and autonomous imbalance play important roles in the pathogenesis of hypertension. Heart rate variability (HRV) and heart rate turbulence (HRT) reflect the autonomic regulation of cardiac function. HRV is the response of autonomic nervous system to external environmental stimuli, and HRT is the response to autonomic nervous function triggered by endogenous ventricular premature beat. Abnormal HRV and HRT reflected autonomous imbalance and were related to worse cardiovascular outcome [2–5]. Abnormal HRV or

HRT was demonstrated in hypertensive patients in previous studies [6–8]. However, there was scantly research on the relationship between HRV, HRT, and blood pressure control with hypertensive patients. The present study analyzed the HRV and HRT between nonhypertensive (N-HP) patients and hypertensive patients and between hypertensive patients with uncontrolled blood pressure and controlled blood pressure after hypertensive medication.

2. Materials and Methods

2.1. Study Population. A total of 120 consecutive hospitalized hypertensive patients and 80 N-HP patients were included in this retrospective study from June 2016 to June 2018. The hypertensive patients were divided into controlled

blood pressure (n=66) and uncontrolled blood pressure (n=54) groups according to their blood pressure on admission.

Patients with Diabetes Mellitus (DM), Acute Coronary Syndrome (ACS), valvular heart disease and known non-ischemic cardiomyopathy, atrial fibrillation, atrial flutter, 2nd- or 3rd-degree atrioventricular block, and pacemaker implantation and patients without premature ventricular contraction (PVC) of 24-hour Holter monitoring were excluded. All hypertensive patients received antihypertensive medication. All patients gave informed consent for participation in this study, and the study protocol was approved by the ethical committees of Wuhan Fourth Hospital, Puai Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

2.2. HRV Analysis. All participants underwent 24-hour Holter monitoring (GE MARS Software and Seer Light recording box). Quantitative HRV analysis was performed according to the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [9]. HRV parameters were derived from Holter monitoring including time domain and frequency domain. The following four time domain and four frequency domain indexes were analyzed: standard deviation of NN intervals (SDNN), standard deviation of all 5-minute average NN intervals (SDANN), square root of mean of the sum of squares of successive NN interval differences (rMSSD), number of successive NN intervals differing by > 50ms divided by the total number of successive NN intervals (pNN50), very low frequency (VLF) at frequency between 0.0033 and 0.04 Hz, low frequency (LF) at frequency between 0.04 and 0.15 Hz, high frequency (HF) at frequency between 0.15 and 0.4 Hz, and low frequency/high frequency ratio (LF/HF).

2.3. HRT Analysis. HRT parameters were also derived from Holter monitoring including turbulence onset (TO) and turbulence slope (TS). TO was the amount of sinus acceleration following a PVC. TO was expressed as a percentage and was calculated with the following formula: TO (%) = $100 \times [(RR1 + RR2) - (RR{-1} + RR{-2})]/(RR{-1} + RR{-2})$, where RR1 and RR2 were the first and second sinus RR intervals after the PVC, and RR−1 and RR−2 were the first and second sinus intervals preceding the PVC. TO value < 0% indicated early sinus acceleration and was considered normal. TO ≥ 0% indicated that normal sinus heart rate acceleration phenomenon after PVC disappeared and was described as abnormal [5]. TS was late deceleration phenomenon of sinus rhythm after PVC following the sinus acceleration. TS was defined as the maximum regression slope measured on any 5- consecutive sinus beats within the first 15-sinus intervals after a PVC. TS could not be calculated when there were fewer than 15-sinus beats after the PVC. TS value > 2.5 ms/RR interval indicated the normal expected late deceleration. TS ≤ 2.5 ms/RR interval is described as abnormal [5]. TO and TS were computed as an average of the responses to all PVC on Holter record.

2.4. Statistical Analysis. Continuous data were presented as mean ± standard deviation (SD). Normal distribution of continuous variables was performed by Kolmogorov-Smirnov test. Continuous variables with normal distribution were assessed by Student's *t*-test. Nonnormal distribution data were tested by two-tailed Mann–Whitney *U* test. The chi-square test was used to compare categorical variables as percentages. The risk factors for hypertension were determined by multivariate logistic regression model after adjusting for age, gender, and beta-blockers use. Spearman correlation analysis of the hypertensive patients was performed between HRV and HRT. *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS (version 22.0) for Windows (SPSS).

3. Results

3.1. Clinical Features of Patients in N-HP and HP Groups. BMI, triglyceride level, interventricular septum (IVS) thickness, and incidence of stable CAD were significantly higher in the HP group compared to the N-HP group. Blood pressure on admission was significantly higher in the HP group compared to the N-HP group. The proportions of beta-blockers and diuretics uses were higher in the HP group than in the N-HP group (Table 1). TS, rMSSD, pNN50, VLF, LF, and HF values were significantly lower in the HP group than in the N-HP group (Figure 1). Multiple regression analysis showed that history of stable CAD, higher BMI, and reduced TS, rMSSD, pNN50, LF, and HF values were risk factors of hypertension after adjusting for gender, age, and beta-blockers use (Table 2).

3.2. Clinical Features of Hypertensive Patients with Controlled and Uncontrolled Blood Pressure. The percentage of hypertensive patients receiving combined antihypertensive drug therapy was significantly higher and percentage of patients treating with monotherapy was significantly lower in hypertensive patients with uncontrolled blood pressure compared to hypertensive patients with controlled blood pressure (Table 3). TS, rMSSD, pNN50, VLF, LF, and HF values were significantly lower in hypertensive patients with uncontrolled blood pressure compared to hypertensive patients with controlled blood pressure (Figure 2). Multiple logistic regression analysis showed that reduced TS, rMSSD, pNN50, VLF, LF, and HF values were risk factors for blood pressure control after adjusting for age, gender, and beta-blockers use (Table 4).

3.3. Spearman Correlation of HRV and HRT for Hypertensive Patients. Spearman correlation analysis of the hypertensive patients showed that LF and LF/HF were negatively correlated with TO, while SDNN, SDANN, rMSSD, PNN50, VLF, LF, and HF were positively correlated with TS (Table 5).

4. Discussion

The present study found that TS, rMSSD, pNN50, VLF, LF, and HF values were significantly lower in hypertensive patients compared to N-HP patients, and TS, rMSSD,
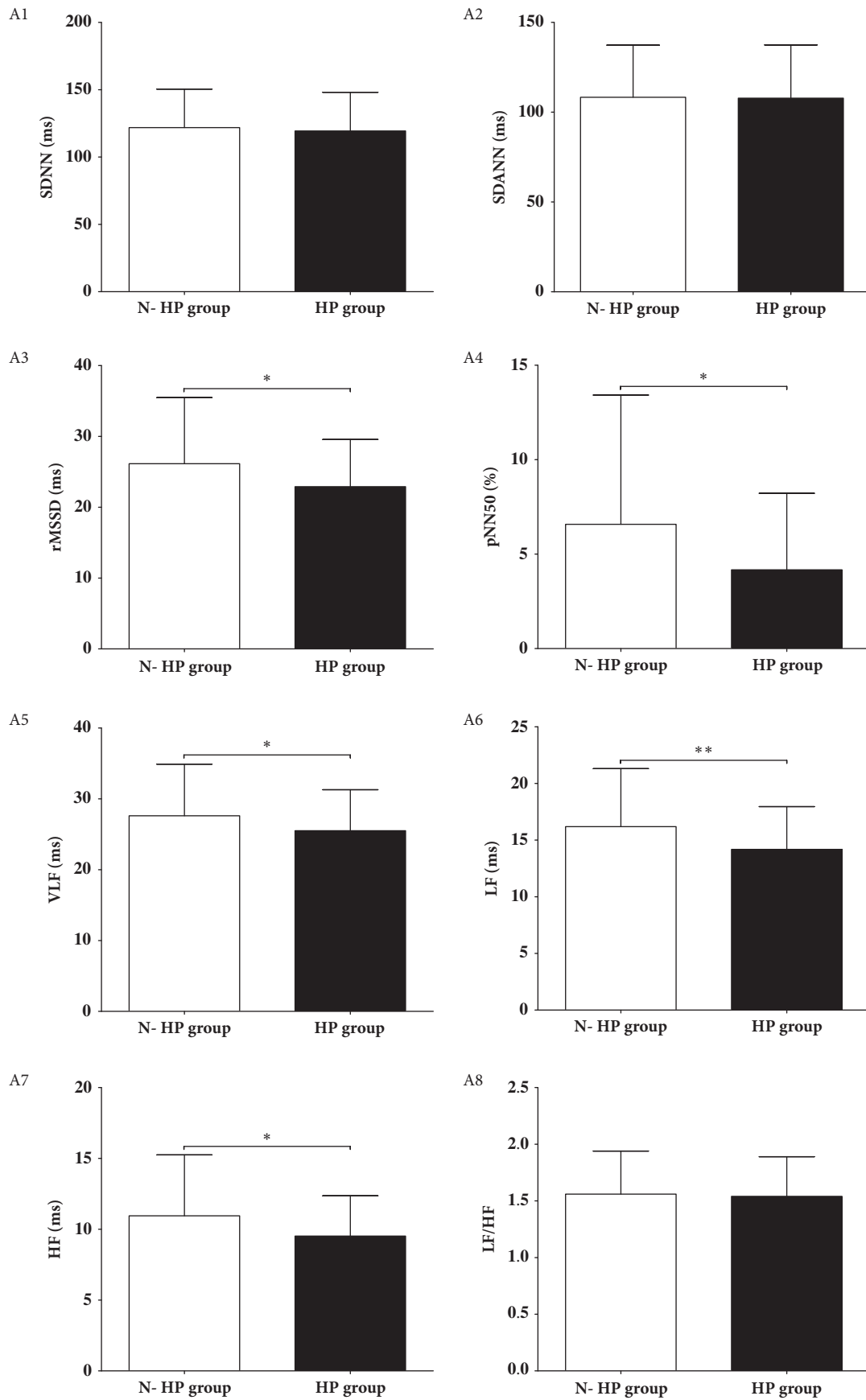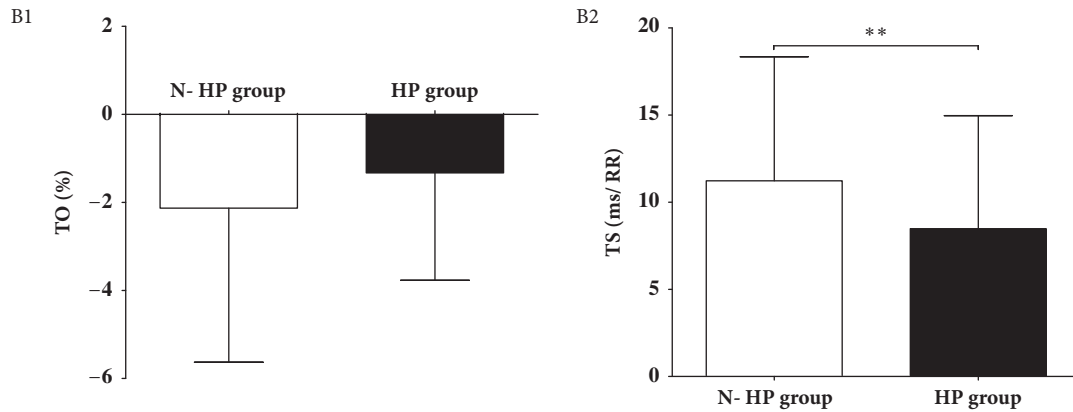
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FIGURE 1: HRV and HRT analysis of N-HP and HP groups; $*P<0.05$; $**P<0.01$. HRV, heart rate variability; HRT, heart rate turbulence; N-HP, nonhypertensive; HP, hypertensive; SDNN, standard deviation of NN intervals; SDANN, standard deviation of all 5-minute average NN intervals; rMSSD, square root of mean of the sum of squares of successive NN interval differences; pNN50, number of successive NN intervals differing by >50ms divided by the total number of successive NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; TO, turbulence onset; TS, turbulence slope.

TABLE 1: Clinical characteristic of N-HP group and HP group.

	N-HP group (n=80)	HP group (n=120)	P value
Age (yr)	56.66±6.62	58.05±7.55	0.183
Male gender (n, %)	39/80 (48.5%)	54/120 (45.0%)	0.602
BMI (kg/m^2)	23.60±2.78	25.20±3.29	<0.0001
Smoker (n, %)	21/80 (26.3%)	40/120 (33.3%)	0.286
Stable CAD (n, %)	12/80 (15.0%)	37/120 (30.8%)	0.011
Dyslipidemia (n, %)	64/80 (80.0%)	105/120 (87.5%)	0.151
Systolic blood pressure (mmHg)	118.50±11.75	134.98±14.95	<0.0001
Diastolic blood pressure (mmHg)	76.10±7.48	81.98±10.15	<0.0001
Heart rate (bpm)	74.18±6.62	73.11±8.16	0.307
Creatinine (μM)	67.44±16.33	67.34±14.63	0.839
CHOL (mM)	4.67±0.91	4.83±1.00	0.228
TG (mM)	1.59±0.98	2.13±2.10	0.002
LDL-c (mM)	2.96±0.83	2.92±0.82	0.742
HDL-c (mM)	1.09±0.25	1.10±0.27	0.848
Ejection fraction (%)	61.61±4.95	61.91±5.17	0.657
LVEDd (cm)	4.39±0.39	4.40±0.44	0.843
IVS (cm)	0.93±0.12	0.99±0.19	0.010
Medication			
Bata-blockers use (n, %)	23/80 (28.8%)	60/120 (50.0%)	0.003
Diuretics use (n, %)	0/80 (0.0%)	12/120 (10.0%)	0.009

N-HP, nonhypertensive; HP, hypertensive; BMI, body mass index; CAD, coronary artery disease; CHOL, cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; LVEDd, left ventricular end diastolic diameter; IVS, interventricular septum.

pNN50, VLF, LF, and HF values were significantly lower in hypertensive patients with uncontrolled blood pressure compared to hypertensive patients with controlled blood pressure. Our study results thus indicate impaired autonomic nervous function in hypertensive patients, especially in hypertensive patients with uncontrolled blood pressure despite guideline recommended antihypertensive medications. To the best of our knowledge, this is the first study describing the association between autonomic nervous function, evaluated by HRV and HRT changes, and blood pressure control in hypertensive patients.

4.1. Reduced HRV and HRT in Hypertensive Patients.

HRV and HRT changes could reflect sympathetic and vagal function in hypertensive patients. HRV reflects the fluctuation of heart rate as time changes in response to external environmental stimulation; HRV changes were related to various cardiovascular diseases [3]. HRT reflects the start
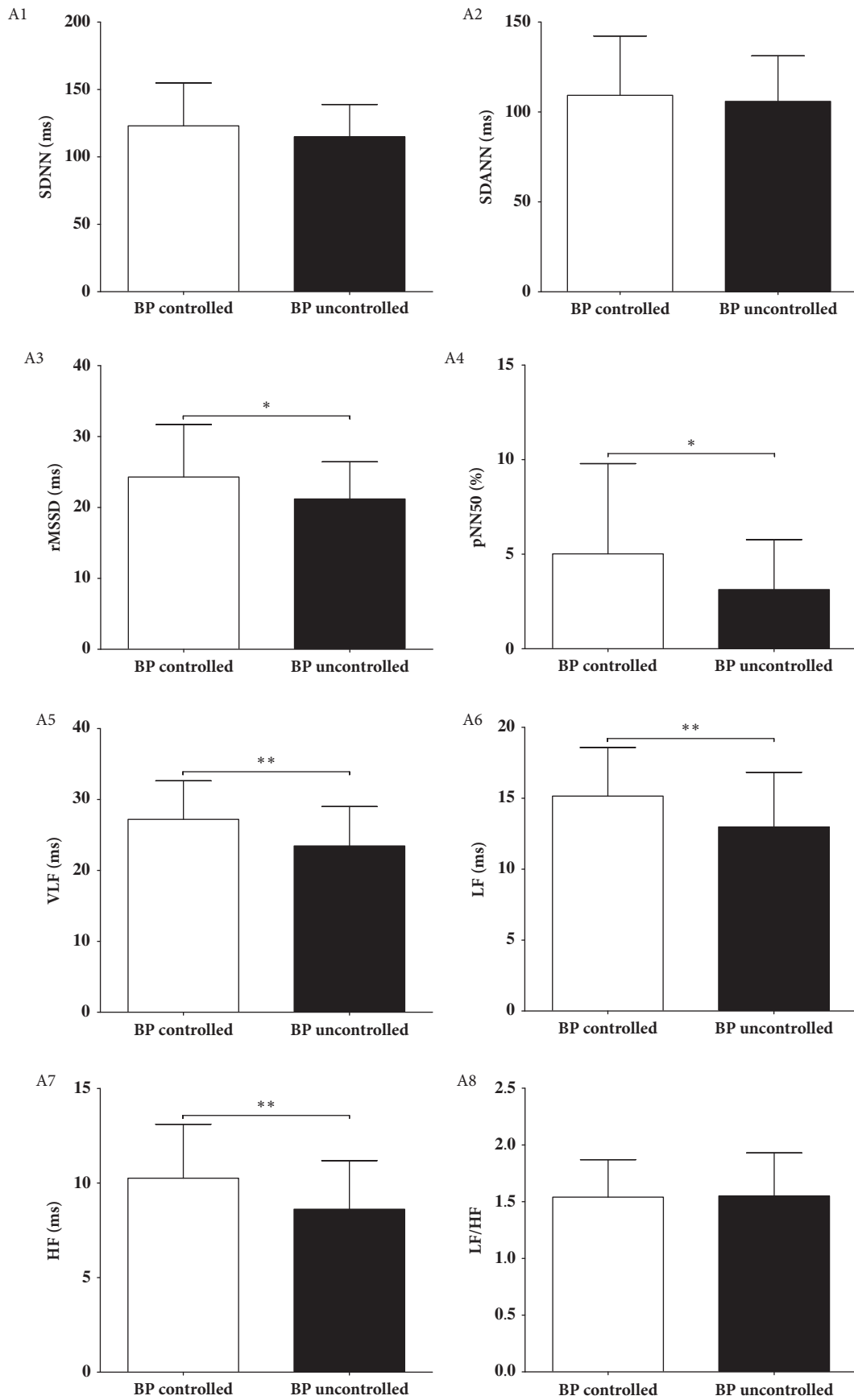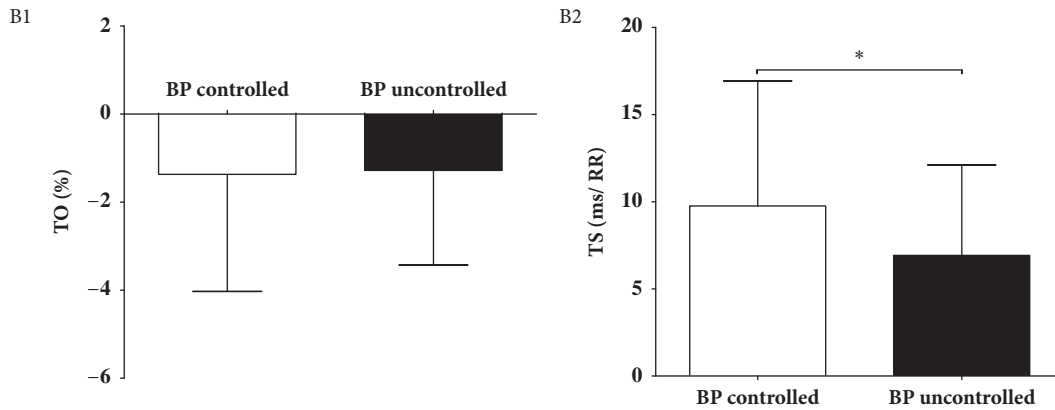
Figure 2: Continued.

FIGURE 2: HRV and HRT analysis of BP controlled and BP uncontrolled groups, $*P<0.05$; $**P<0.01$. HRV, heart rate variability; HRT, heart rate turbulence; BP, blood pressure; SDNN, standard deviation of NN intervals; SDANN, standard deviation of all 5-minute average NN intervals; rMSSD, square root of mean of the sum of squares of successive NN interval differences; pNN50, number of successive NN intervals differing by >50ms divided by the total number of successive NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; TO, turbulence onset; TS, turbulence slope.

TABLE 2: Multivariate logistic regression results for risk of hypertension.

	B	S.E	Wald	P value	Exp	95% CI lower limit	95% CI upper limit
BMI	0.196	0.053	13.788	0.000	1.217	1.097	1.350
Stable CAD	0.832	0.395	4.431	0.035	2.297	1.059	4.982
TG	0.413	0.163	6.387	0.011	1.511	1.097	2.082
rMSSD (ms)	0.044	0.020	4.804	0.028	1.045	1.005	1.086
pNN50 (%)	0.070	0.031	5.249	0.022	1.073	1.010	1.139
VLF (ms)	0.039	0.024	2.716	0.099	1.041	0.993	1.091
LF (ms)	0.100	0.037	7.187	0.007	1.105	1.027	1.189
HF (ms)	0.096	0.046	4.356	0.037	1.100	1.006	1.203
TS (ms/ RR)	0.055	0.023	5.684	0.017	1.057	1.010	1.106

BMI, body mass index; CAD, coronary artery disease; TG, triglyceride; rMSSD, square root of mean of the sum of squares of successive NN interval differences; pNN50, number of successive NN intervals differing by >50ms divided by the total number of successive NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; TS, turbulence slope.

acceleration and the late deceleration of the heart rate after ventricular premature contraction and refers the endogenous stimulus triggered pressure reflex regulation and could also be used to evaluate the balance and coordination of the cardiac autonomic nervous system [5]. Combined analysis with HRV and HRT parameters makes it possible to comprehensively evaluate the autonomic nervous system regulation and response status to internal and external stimuli in hypertensive patients. Pal and colleagues [7] demonstrated enhanced sympathetic nerve activity and inhibited vagal activity in prehypertensive patients and found that the vagal inhibition was more prominent than sympathetic overactivity in hypertensive patients. Erdem [10] explored the relationship between autonomic nervous regulation and blood pressure in prehypertensive patients and found that TO was significantly higher and TS was significantly lower in nondipper blood pressure group than in dipper blood pressure group, hinting at impaired autonomous balance in prehypertensive patients with nondipper blood pressure. Another study [11] reported that heart rate was increased and HRV was decreased in

patients with refractory hypertension, suggesting that overactivation of the sympathetic nervous system might play an important role in patients with refractory hypertension. In a previous study [12], we demonstrated significant differences on autonomous balance in hypertensive patients with controlled and uncontrolled blood pressure. The present study showed that TS (reflecting vagus function triggered by endogenous ventricular premature beat [13]), rMSSD (reflecting vagus function by external environmental stimuli [14]), pNN50 (reflecting vagus function by external environmental stimuli [14]), VLF (reflecting sympathetic activity by external environmental stimuli [15]), LF (reflecting balance of sympathetic and vagal activity [14]), and HF (reflecting vagus function by external environmental stimuli [14]) values were significantly lower in hypertensive patients compared to N-HP patients, and TS, rMSSD, pNN50, VLF, LF, and HF values were also significantly lower in hypertensive patients with uncontrolled blood pressure compared to hypertensive patients with controlled blood pressure. This novel finding demonstrated that autonomic nervous function was impaired

TABLE 3: Clinical characteristics of hypertensive patients with controlled blood pressure group and uncontrolled blood pressure group.

	BP controlled group (n=66)	BP uncontrolled group (n=54)	P value
Age (yr)	57.03±6.81	59.30±8.26	0.109
Male gender (n, %)	27/66 (40.9%)	27/54 (50.0%)	0.319
BMI (kg/m^2)	25.19±3.34	25.22±3.25	0.954
Smoker (n, %)	20/66 (30.3%)	20/54 (37.0%)	0.436
Stable CAD (n, %)	18/66 (27.3%)	19/54 (35.1%)	0.350
Dyslipidemia (n, %)	58/66 (87.9%)	47/54 (87.0%)	0.890
SBP (mmHg)	124.97±9.72	147.20±10.45	<0.0001
DBP (mmHg)	78.02±7.43	86.82±10.97	0.000
Heart rate (bpm)	72.35±8.27	74.03±8.00	0.364
Creatinine (μM)	67.14±14.87	67.59±14.46	0.867
CHOL (mM)	4.83±0.93	4.84±1.08	0.945
TG (mM)	2.00±1.49	2.29±2.68	0.663
LDL-c (mM)	2.97±0.81	2.86±0.84	0.472
HDL-c (mM)	1.11±0.25	1.09±0.30	0.436
Ejection fraction (%)	62.33±4.78	61.39±5.60	0.321
LVEDd (cm)	4.40±0.48	4.41±0.39	0.907
IVS (cm)	1.00±0.15	1.00±0.22	0.891
Medication			
Bata-blockers (n, %)	32/66 (48.5%)	28/54 (51.9%)	0.714
ACEI (n, %)	14/66 (21.2%)	12/54 (22.2%)	0.894
ARBs (n, %)	19/66 (28.8%)	23/54 (42.6%)	0.115
CCB (n, %)	37/66 (56.1%)	39/54 (72.2%)	0.068
Diuretics (n, %)	6/66 (9.1%)	6/54 (11.1%)	0.714
Categories of drugs			0.021
Monotherapy (n,%)	32/66 (48.5%)	15/54 (27.7%)	
≥Two-drug therapy (n, %)	34/66 (51.5%)	39/54 (72.2%)	

BP, blood pressure; BMI, body mass index; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHOL, cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; LVEDd, left ventricular end diastolic diameter; IVS, interventricular septum; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; CCB, calcium channel blocker.

TABLE 4: Multivariate logistic regression results for risk of uncontrolled blood pressure.

	B	S.E	Wald	P value	Exp	95% CI lower limit	95% CI upper limit
rMSSD (ms)	0.073	0.032	5.363	0.021	1.075	1.011	1.144
pNN50 (%)	0.131	0.058	5.130	0.024	1.140	1.017	1.277
VLF (ms)	0.128	0.038	11.358	0.001	1.136	1.055	1.225
LF (ms)	0.166	0.058	8.245	0.004	1.181	1.054	1.321
HF (ms)	0.213	0.076	7.957	0.005	1.238	1.067	1.435
TS (ms/ RR)	0.071	0.034	4.453	0.035	1.073	1.005	1.147

rMSSD, square root of mean of the sum of squares of successive NN interval differences; pNN50, number of successive NN intervals differing by >50ms divided by the total number of successive NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; TS, turbulence slope.

in hypertensive patients compared to N-HP patients. Moreover, autonomic nervous function damage was more severe in hypertensive patients with uncontrolled blood pressure than in hypertensive patients with controlled blood pressure, as expressed by sympathetic overactivity and vagal withdrawal triggered by external environmental stimuli and vagal withdrawal triggered by endogenous ventricular premature beat. In our study, the percentage of hypertensive patients receiving combined antihypertensive drug therapy was significantly higher and percentage of patients treated with monotherapy was significantly lower in hypertensive patients with uncontrolled blood pressure compared to hypertensive patients with controlled blood pressure, indicating that the uncontrolled blood pressure observed in our patient cohort is probably not due to the insufficient hypertensive medication; future studies are warranted to explore the role of the

TABLE 5: Spearman correlation analysis of HRV and HRT in HP patients.

	TO		TS	
	r value	P value	r value	P value
SDNN	-0.008	0.930	0.298	0.001
SDANN	0.023	0.800	0.260	0.004
rMSSD	0.006	0.945	0.292	0.001
pNN50	-0.012	0.895	0.228	0.012
VLF	-0.143	0.120	0.438	<0.0001
LF	-0.237	0.009	0.441	<0.0001
HF	-0.027	0.767	0.343	<0.0001
LF/HF	-0.241	0.008	0.095	0.301

HRV, heart rate variability; HRT, heart rate turbulence; HP, hypertensive; SDNN, standard deviation of NN intervals; SDANN, standard deviation of all 5-minute average NN intervals; rMSSD, square root of mean of the sum of squares of successive NN interval differences; pNN50, number of successive NN intervals differing by >50ms divided by the total number of successive NN intervals; VLF, very low frequency; LF, low frequency; HF, high frequency; TO, turbulence onset; TS, turbulence slope.

more severe autonomous function impairment in hypertensive patients with uncontrolled blood pressure despite the treatment of guideline recommended antihypertensive medications and to see if options targeting the autonomic nervous function might help the blood pressure control on top of combined antihypertensive therapy [16].

Previous studies found that DM and beta-blockers use might affect the HRV [15, 17]. Patients with DM were thus excluded in our study. Results of logistic regression analysis showed that reduced TS, rMSSD, pNN50, VLF, LF, and HF values were risk factors for uncontrolled blood pressure after adjusting for age, gender, and beta-blockers use. Therefore, the difference in HRV and HRT values between the uncontrolled and controlled blood pressure groups was unlikely induced by beta-blockers use.

HRV mainly reflected the interaction between neural modulatory and sinus node function, while HRT could be considered as parameter reflecting the physiological response to endogenous stimulus. Spearman correlation analysis between HRV and HRT showed that LF and LF/HF were negatively correlated with TO, and SDNN, SDANN, rMSSD, PNN50, VLF, LF, and HF were positively correlated with TS, which suggested the close correlation between HRV and TS, and HRV and HRT could be considered as complementary parameters reflecting autonomic nervous function change.

4.2. Clinical Implications. Impaired autonomic function played an important role in the pathogenesis of hypertension. Long-term sympathetic excitation might lead to left ventricular remodeling and atherosclerosis. Poreba et al. [8] found that TO was significantly higher and TS was significantly lower in hypertensive patients with left ventricular hypertrophy than in hypertensive patients without left ventricular hypertrophy. Therefore, the detection of autonomic nervous function in hypertensive patients might be useful in predicting the target organ damage in hypertensive patients. Abnormal HRV and HRT in hypertensive patients might suggest the presence of autonomic nervous system dysfunction. The present results found abnormal HRV and HRT in hypertensive patients, especially in hypertensive patients with uncontrolled blood pressure. It is thus clinically

important to monitor HRV and HRT during antihypertensive therapy, aiming to improve the autonomic nervous system function in hypertensive patients, which might reduce the incidence of target organ damage and improve the prognosis of hypertensive patients.

4.3. Study Limitations. There were some limitations in this study. First, this was a retrospective single-center clinical study with a small number of patients. Our results need to be confirmed by a multicenter prospective clinical study with larger patient cohort to explore the impact of autonomic nervous dysfunction on prognosis of hypertensive patients. Second, HRV and HRT evaluation was not suitable to hypertensive patients with nonsinus rhythm such as atrial fibrillation, atrial flutter or pacemaker implantation, or 2nd- or 3rd-degree atrioventricular block and without PVC on Holter monitoring. Third, we did not quantify cardiac remodeling parameters including left ventricular posterior wall thickness and diastolic function parameters as E/A and E/e' in this patient cohort. Finally, this study did not analyze potential impact of the disease stage as well as the duration of antihypertensive medication on HRV and HRT because many elderly patients in this patient cohort could not provide us with the inquired data. Above study limitations should be considered when interpreting results demonstrated in this study.

5. Conclusions

The present study shows that autonomic nervous dysfunction, as expressed by reduced HRV and HRT, exists in hypertensive patients, especially in hypertensive patients with uncontrolled blood pressure. Monitoring HRV and HRT parameters, which jointly reflect autonomic nervous system's regulation and response to internal and external stimuli, might be helpful to evaluate the autonomic nervous function status of the patients and supply useful information to optimize therapeutic efficacy aiming to improve autonomic nervous function balance for hypertensive patients. Future studies are warranted to explore if targeting the autonomic nervous function on top of antihypertensive medication

might obtain better clinical efficacy on blood pressure control for patients with refractory hypertension.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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