

## Original Article

# The association and clinical predictive value of resting heart rate and hypertension on cardiovascular autonomic neuropathy in general population

Jin Zhang<sup>1</sup>, Yuweng Jiang<sup>1</sup>, Fangfang Zeng<sup>1</sup>, Haiming Shi<sup>1</sup>, Zihui Tang<sup>2</sup>

<sup>1</sup>Department of Cardiology, Fudan University Huashan Hospital, Shanghai, China; <sup>2</sup>Department of Endocrinology and Metabolism, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China

Received November 15, 2015; Accepted February 2, 2016; Epub June 15, 2016; Published June 30, 2016

**Abstract:** Objective: The purpose of this study was to explore the extent of associations of cardiovascular autonomic (CAN) with hypertension (HT) and resting heart rate (HR), and to evaluate the predictive value of HT combined with HR on CAN in a large sample derived from a Chinese population. Methods: We conducted a large-scale, cross-sectional study among 2092 subjects. CA function was measured by using short-time heart rate variable test. CAN was diagnosed on at least two abnormal CA function tests. The associations of CAN with HT and resting HR were assessed by a multivariate logistic regression (MLR) analysis. The area under the receiver-operating characteristic curve was used to evaluate the predictive performances of both factors. Results: A tendency toward increased CAN prevalence with increasing resting HR was reported (P for trend < 0.001). MLR analysis showed that HT and resting HR were very significantly and independently associated with CAN ( $\beta = 0.439$  for HT and  $\beta = 0.946$  for HR,  $P < 0.001$  for both). Resting HR and it combined HT (HT-HR) strongly predicted CAN (AUC = 0.719, 95% CI: 0.690-0.748,  $P < 0.001$  for resting HR and AUC = 0.743 95% CI: 0.715-0.770,  $P < 0.001$  for HT-HR). Conclusion: Our findings signify that, in the general Chinese population, HT and resting HR had a high value in predicting CAN.

**Keywords:** Hypertension, resting heart rate, cardiovascular autonomic neuropathy, association, predictive value

## Introduction

Hypertension (HT) is a chronic medical condition in which the blood pressure in the arteries is elevated, which leads to heart to work harder than normal to circulate blood through the blood vessels [1]. Currently, nearly one billion people or ~26% of the adult population of the world had hypertension, and the disease was common in developed and undeveloped countries [2]. Hypertension is a major risk factor for stroke and coronary heart disease and is a cause of chronic kidney disease. Moreover, moderate elevation of arterial blood pressure is associated with a shortened life expectancy [2]. The prevalence of cardiovascular autonomic neuropathy (CAN) is rapidly growing in all populations worldwide, particularly in the developing world [3, 4]. The disease is not only a major factor in the cardiovascular complications of diabetes mellitus (DM) [5], but also

affects many other majority segments of the general population, such as the elderly, patients with HT, metabolic syndrome (MetS) and connective tissue disorders [3, 6-8]. CAN has become a major health concern in China following recent, rapid changes in lifestyles. In diabetic patients, the prevalence of CAN was 30-60% [5]. Individuals with previously undiagnosed CA dysfunction have an unfavorable cardiovascular risk profile, especially in terms of sudden death, indicating a higher risk of cardiovascular disease [9, 10].

Previous studies indicate that in diabetic patients, increased resting HR is an early indicator of CAN, and a strong association between HR and CAN was found [11, 12]. Moreover, resting HR is considered a critical clinical early biomarker for CAN in diabetic patients. HT also was reported to strongly associate with CAN in diabetic and non-diabetic patients with HT in

previous studies [13-16]. In our previous study, in a Chinese population, Blood pressure (BP) or HT was reported to be associated with components of CA function [17]. In addition, our previous study demonstrated that resting HR and DM or MetS associated with CAN in general Chinese population [18, 19]. Furthermore, it is important to clarify the relationship of CAN with HT and resting HR in the general population, as this information can help clinicians in the prediction, prevention and treatment of CAN.

However, at the population level, the extent of the associations between CAN and HT and/or HR remains largely unexplored. In addition, in the general population, the role of HT combined with resting HR in predicting CAN has not been well defined. The purpose of this study is to evaluate the extent of CAN's associations with HT and resting HR, and to assess the predictive value of HT combined with HR for CAN in a large sample derived from a Chinese population.

### Materials and methods

#### *Study population*

We performed a CAN factor survey on a random sample of the Chinese population. Participants were recruited from rural and urban communities in Shanghai. Survey participants with undiagnosed CAN, aged 30-80 years, were included in this study. A total of 3,012 subjects were invited to a screening visit between 2011 and 2012. Some subjects were excluded from the study to eliminate potential confounding factors that may have influenced their CA function. Briefly, the exclusion criteria were as follows: 1) history or findings of arrhythmia, hyperthyroidism or hypothyroidism; 2) pregnancy or lactation; 3) serious chronic disease, heart failure and cancer; 4) medication of controlling heart rate such as  $\beta$  receptor inhibitor and/or 5) serious hepatic or renal dysfunctions. Complete baseline data were obtained for 2,092 (69.46%) of the participants. Written consent was obtained from all patients before the study. This study was approved by the Ethics Committee of the Huashan Hospital and Tongji Hospital affiliated to Tongji University, Shanghai, China.

#### *Measurement*

The subjects were interviewed for the documentation of medical histories and medication,

history of smoking habits, laboratory assessment of cardiovascular disease risk factors and standardized examination for heart rate variability (HRV). All study subjects underwent a complete clinical baseline characteristics evaluation after an eight-hour fast, which included: 1) history and physical examination; 2) heart rate and blood pressure; 3) fasting serum glucose and insulin; 4) oral glucose tolerance test (OGTT) and 5) fasting plasma lipids. Body mass index (BMI) was calculated with weight in kilograms divided by the square of height in meters. Physicians measured systolic and diastolic BP values from the left arm while participants were seated. Fasting plasma glucose (FPG) was quantified by the glucose oxidase procedure; HbA1c was measured by ion-exchange high-performance liquid chromatography (HPLC; Bio-Rad, Hercules, CA, USA). The homeostasis model assessment insulin resistance estimate (HOMA-IR) was calculated as serum glucose (mmol/L) multiplied by plasma insulin (U/mL) and divided by 22.5. Serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglyceride (TG) levels, serum creatinine (SCr), and uric acid (UA) were measured by an enzymatic method with a chemical analyzer (Hitachi 7600-020, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula. The day-to-day and inter-assay coefficients of variation at the central laboratory in our hospital for all analyses were between 1% and 3%. Short-term HRV has good reproducibility and is more practical in its application. In our large-scale population-based study, this test was used to evaluate CA function. HRV were measured non-invasively by power spectral analysis. Before CA function assessment, participants must avoid alcohol, smoking and coffee for 24 hours so as not to influence their resting status. Subjects were studied while awake in the supine position after 20 minutes of rest. Testing times were from 8:00 to 11:00 a.m. A type-I FDP-1 HRV non-invasive detecting system was used with software version 2.0 (Department of Biomedical Engineering of the Fudan University, Shanghai, China). Electrocardiography, respiratory signals, and beat-to-beat blood pressure were continually and simultaneously recorded for 15 minutes through an electrospigmograph transducer (HMX-3C placed on the radial artery of the dominant arm) and an instrument respiration sensor. Short-term HRV analysis was performed for all subjects using a computer-aided

## HT and HR in predicting CAN

**Table 1.** Clinical characteristics of subjects

Variable	Entire sample	Subjects without CAN	Subjects with CAN	P value*
<b>Demographic information</b>				
N	2096	1705	387	
Age (years)	60.42±8.68	59.85±8.64	62.94±8.43	< 0.001
Gender (male, %)	705 (33.7%)	562 (32.96%)	143 (36.95%)	0.134
BMI (kg/m <sup>2</sup> )	24.21±3.37	24.07±3.28	24.84±3.7	< 0.001
WC (cm)	85.07±9.77	84.47±9.62	87.72±9.99	< 0.001
SBP (mmHg)	127.62±18.77	126.39±18.22	133.05±20.19	< 0.001
DBP (mmHg)	79.83±9.74	79.5±9.65	81.31±10.01	0.001
<b>Laboratory measurement</b>				
FPG (mmol/L)	5.53±1.82	5.4±1.58	6.12±2.54	< 0.001
PBG (mmol/L)	7.67±3.63	7.36±3.3	9.07±4.6	< 0.001
HbA1c (%)	6±1.08	5.89±0.92	6.47±1.54	< 0.001
FINS uml	7.19±11.86	6.74±8.03	9.18±21.71	< 0.001
IR (mmol/L)	1.81±3.31	1.64±2.13	2.54±6.22	< 0.001
TC (mmol/L)	5.32±1	5.31±0.98	5.39±1.05	0.142
TG (mmol/L)	1.71±0.98	1.67±0.93	1.9±1.17	< 0.001
HDL (mmol/L)	1.36±0.32	1.36±0.33	1.34±0.32	0.203
LDL (mmol/L)	3.19±0.77	3.18±0.76	3.23±0.81	0.229
SCr (μmol/L)	77.81±26.11	77.65±26.96	78.51±21.98	0.561
UA (μmol/L)	281.21±84.01	280.13±83.47	285.99±86.26	0.216
<b>HRV indices</b>				
HR (bpm)	72.42±10.13	70.77±9.08	79.7±11.26	< 0.001
TP (ms <sup>2</sup> )	873.95±702.47	1000.63±693.2	315.87±410.75	< 0.001
LF (ms <sup>2</sup> )	190.98±207.88	224.34±215.08	43.97±57.29	< 0.001
HF (ms <sup>2</sup> )	183.05±219.43	215.11±229.61	41.82±59.63	< 0.001
LF/HF	1.7±1.98	1.55±1.48	2.37±3.32	< 0.001
<b>Medical history</b>				
Smoking (yes, %)	306 (14.63%)	244 (14.31%)	62 (16.02%)	0.39
MetS (yes, %)	833 (39.82%)	629 (36.89%)	204 (52.71%)	< 0.001
DM (yes, %)	446 (21.33%)	307 (18.02%)	139 (35.92%)	< 0.001
HT (yes, %)	976 (46.65%)	735 (43.11%)	241 (62.27%)	< 0.001

Note: \*Present the difference between subjects with and without cardiovascular autonomic neuropathy (CAN). BMI-Body mass index, WC-waist circumference, SBP-systolic blood pressure, DBP-diastolic blood pressure, FPG-fasting plasma glucose, PBG-plasma blood glucose, FINS-fasting blood insulin, IR-insulin resistance, TC-serum total cholesterol, TG-triglyceride, UA-uric acid, HDL-high-density lipoprotein cholesterol, LDL-low density lipoprotein cholesterol, SCr-serum creatinine, HR-heart rate, TP-total power of variance, LF-low frequency, HF-high frequency, MetS-metabolic syndrome, DM-Diabetes, HT-Hypertension.

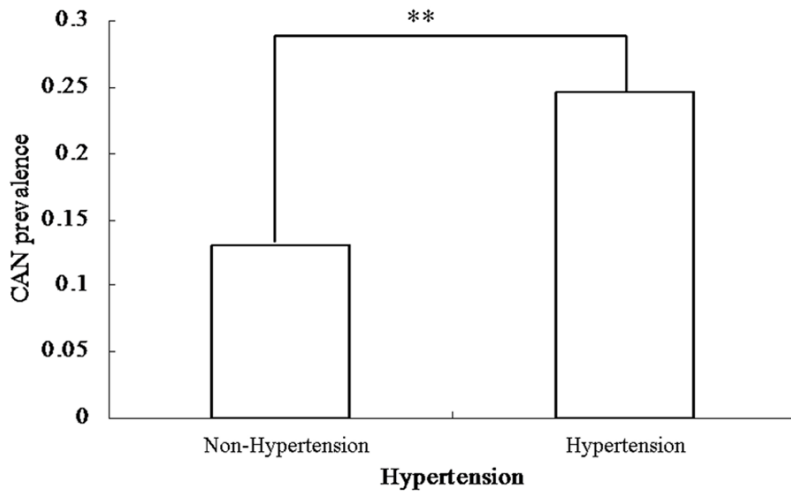
examination and evaluation system for spectral analysis to investigate changes in autonomic regulation.

### Definition

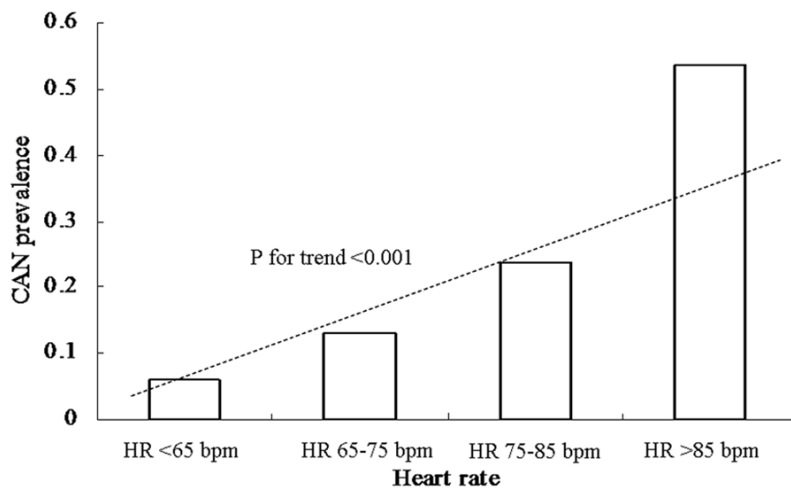
HT was defined as BP  $\geq$  140/90 mmHg, or a history of hypertension medication. BMI was classified based on the Chinese criteria: normal as BMI < 24.0 kg/m<sup>2</sup>; overweight as 24.0 kg/m<sup>2</sup>  $\leq$  BMI < 28.0 kg/m<sup>2</sup>; and obese as BMI  $\geq$  28.0 kg/m<sup>2</sup>. High FPG was defined as FPG  $\geq$  5.6

mmol/L. Center obesity was defined using ethnicity-specific values for waist circumference (WC) of  $\geq$  90 cm in men and  $\geq$  80 cm in women [20]. TG was defined as TG  $\geq$  1.7 mmol/L. HDL was defined as HDL < 0.9 mmol/L in men and HDL < 1.0 mmol/L in women. DM was defined by OGTT and either HbA1c  $\geq$  6.5% or the use of insulin or hypoglycemic medications. MetS was diagnosed according to the updated National Cholesterol Education Program/Adult Treatment Panel III criteria (WHO Western Pacific Region obesity criteria) in individuals meeting

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**Figure 1.** Cardiovascular autonomic neuropathy (CAN) prevalence according to hypertension (HT). The CAN prevalence was 13.08% and 24.69% in respective groups according to HT. *P* value for trend was less than 0.001.



**Figure 2.** Cardiovascular autonomic neuropathy (CAN) prevalence according to resting heart rate (HR). The CAN prevalence was 5.92%, 12.93%, 23.94% and 53.67% in respective groups according to HR. *P* value for trend was less than 0.001.

three or more of the following [20]. CAN was diagnosed based on at least two abnormal cardiovascular autonomic reflex test results from HRV tests [5].

### Statistical analysis

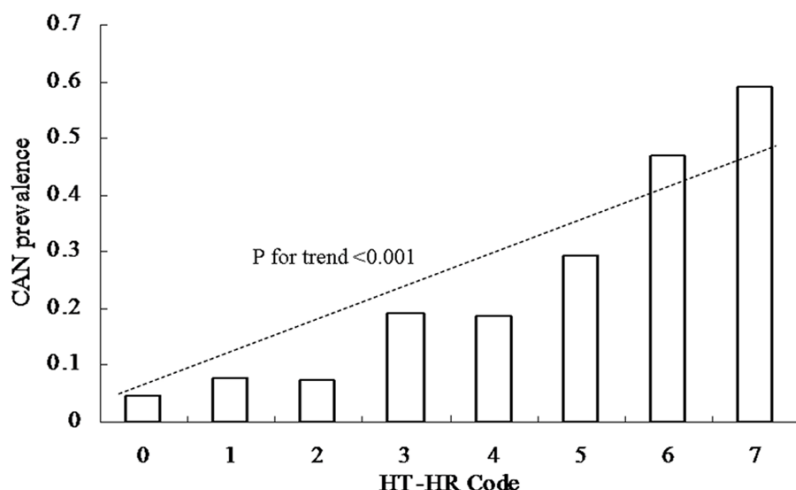
The Kolmogorov-Smirnov test was used to determine whether continuous variables followed a normal distribution. Variables that were not normally distributed were log-transformed to approximate normal distribution for analysis.

The results are expressed as the mean  $\pm$  SD or median, unless otherwise stated. The characteristics of the subjects according to CAN groups were assessed using one-way analysis of variance (ANOVA) for continuous variables and the  $\chi^2$  test for categorical variables.

Univariate logistic regression was performed to determine the variables associated with CAN and to estimate confounding factors possibly disturbing the relationship between CAN and HT or resting HR. Multivariate logistic linear regression (MLR) was carried out to determine the independent contributions of variables to CAN (using subjects without CAN as a reference group). Potential confounding variables were controlled in the regression model. Considering categorized variables easier to be understood and applied in clinical practice, in this analysis the independent variables for CAN were HT (categorized into two groups: code 0 for non-HT and code 1 for HT), resting HR (categorized into four groups: code 0 for < 65; 1 for 65-75; 2 for 75-85; and 3 for > 85 bpm) and HT-HR (categorized into eight groups:

code 0 for HR < 65 bpm and non-HT; 1 for HR < 65 bpm and HT; 2 for HR 65-75 bpm and non-HT; 3 for HR 65-75 bpm and HT; 4 for HR 75-85 bpm and non-HT; 5 for HR 75-85 bpm and HT; 6 for HR > 85 bpm and non-HT; 7 for HR > 85 bpm and HT). The predictive performance of the HT-HR was evaluated using the area under the curve (AUC) in a receiver operating characteristics (ROC) curve. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the relative risk of HT, HR or HT-HR with CAN. The results were analyzed using the

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**Figure 3.** Cardiovascular autonomic neuropathy (CAN) prevalence according to the variable of hypertension (HT) combined with resting heart rate (HT-HR). The CAN prevalence was 4.76, 7.65, 7.36, 19.22, 18.90, 29.30, 46.88 and 59.02% in respective groups according to HT-HR. *P* value for trend was less than 0.001.

Statistical Package for Social Sciences for Windows, version 16.0 (SPSS, Chicago, IL, USA). The tests were two-sided, and a *p* value of < 0.05 was considered significant.

### Results

The baseline clinical characteristics of the 2,902 subjects were grouped according to CAN (**Table 1**). The entire sample included 705 men and 1,387 women (mean age 60.42±8.68 years; **Table 1**). A total of 387 (18.51%) subjects had CAN. The mean FPG, TC and TG levels in the total sample were 5.53 mmol/L, 5.32 mmol/L and 1.71 mmol/L, respectively. The HRV indices decreased with age (data not shown). Most HRV indices were lower in subjects with CAN compared with those without CAN (*P* < 0.01 for all). The HR of subjects with CAN was very significantly higher than that of subjects without CAN (79.70 bpm vs. 70.77 bpm, *P* < 0.001). The prevalence of HT, DM and MetS in the entire sample was 46.65%, 21.33%, and 39.82%, respectively.

The CAN prevalence was 13.08 and 24.69% in the non-HT and HT groups, respectively. The CAN prevalence significantly increased in patients with the HT (*P* < 0.001, **Figure 1**). CAN prevalence was 5.92, 12.93, 23.94 and 53.67% in the respective groups according to HR (**Figure 2**). There was an increased CAN prevalence trend in groups with increased HR (*P* for trend < 0.001). In addition, CAN preva-

lencesignificantlydifferedamong the groups according to the categorical variable of HT-HR (code 0 = 4.76% and 7 = 59.02%; **Figure 3**). Interestingly, there was similar CAN prevalence to be found in subjects with HT-HR of 1 and 2 (7.65% vs. 7.36%; **Figure 3**). Another similar CAN prevalence also reported in subjects with HT-HR of 3 and 4 (19.22% vs. 18.90%; **Figure 3**). As the HT-HR score increased, the CAN prevalence also increased (*P* for trend < 0.001; **Figure 3**).

To estimate the potential risk factors of CAN, univariate analysis was performed

in the entire sample. These potential risk factors contained the demographic parameters, blood glucose, and insulin function parameters as well as lipid profiles and medical history factors. The results indicate that these potential risk factors-age, BMI, WC, SBP, DBP, FPG, PBG, HbA1c, FINS, IR, TG, HR, HT, DM and MetS-were significantly associated with CAN (*P* < 0.05 for all parameters; **Table 2**). The both variables of HR and HT were very significantly associated with CAN in the univariate analysis model.

MLR analysis was carried out to determine the extent to which CAN was associated with HT and HR. HT and HR remained very significantly associated with CAN after adjustments for age, gender, smoking, BMI, IR, TG, UA and DM (*P* < 0.001 for HT and HR, respectively). In subjects with HR ranged from 65 to 75 bpm, the OR of CAN was 2.576 (95% CI, 2.238-2.964; *P* < 0.001; **Table 3**) compared to subjects with HR < 65 bpm. And in subjects with HT, the OR of CAN was 1.552 (95% CI, 1.195-2.015; *P* < 0.001; **Table 3**) compared to subjects with non-HT. In addition, a very significant association between HT-HR and CAN was found by using MLR adjustment for potential confounds including age, gender, smoking, BMI, IR, TG, UA and DM (*P* < 0.001). In subjects with HT-HR of 1, the OR of CAN was 1.612 (95% CI, 1.510-1.722; *P* < 0.001; **Table 3**) compared to subjects with HT-HR of 0.



## HT and HR in predicting CAN

**Table 2.** Univariate logistic regression analysis for cardiovascular autonomic neuropathy

Variable	$\beta$	SE	P value	OR	95% CI
Age	0.042	0.007	< 0.001	1.043	1.029-1.103
Gender	0.176	0.117	0.134	1.192	0.947-1.547
BMI	0.066	0.016	< 0.001	1.068	1.034-1.046
WC	0.034	0.006	< 0.001	1.034	1.023-1.024
SBP	0.018	0.003	< 0.001	1.018	1.012-1.030
DBP	0.019	0.006	0.001	1.019	1.007-1.261
FPG	0.178	0.027	< 0.001	1.195	1.133-1.149
PBG	0.111	0.014	< 0.001	1.117	1.087-1.722
HbA1c	0.392	0.077	< 0.001	1.48	1.271-1.026
FINS	0.014	0.006	0.015	1.014	1.003-1.159
IR	0.091	0.029	0.001	1.095	1.036-1.212
TC	0.082	0.056	0.142	1.086	0.973-1.369
TG	0.213	0.051	< 0.001	1.238	1.119-1.129
HDL	-0.225	0.177	0.203	0.798	0.564-1.259
LDL	0.088	0.073	0.229	1.092	0.946-1.005
UA	0.001	0.001	0.216	1.001	0.999-1.108
Smoking	0.133	0.155	0.39	1.142	0.843-2.733
DM	0.936	0.123	< 0.001	2.550	2.003-3.156
MetS	0.646	0.114	< 0.001	1.907	1.527-1.307
HT	0.779	0.116	< 0.001	2.178	1.736-3.248
HR	0.952	0.068	< 0.001	2.590	2.267-2.565
HT-HR	0.488	0.033	< 0.001	1.628	1.526-1.738

Note: Cardiovascular autonomic neuropathy (CAN);  $\beta$ -regression coefficient, SE-standard error, OR-odds ratio, CI-confidence interval; BMI-Body mass index, WC-waist circumference, SBP-systolic blood pressure, DBP-diastolic blood pressure, FPG-fasting plasma glucose, PBG-plasma blood glucose, FINS-fasting blood insulin, IR-insulin resistance, TC-serum total cholesterol, TG-triglyceride, UA-uric acid, HDL-high-density lipoprotein cholesterol, LDL-low density lipoprotein cholesterol, SCr-serum creatinine, HR-heart rate, TP-total power of variance, LF-low frequency, HF-high frequency, MetS-metabolic syndrome, HT-Hypertension, DM-Diabetes.

**Table 3.** Multivariate logistic regression analysis for cardiovascular autonomic neuropathy

Model	Variable	$\beta$	SE	P value	OR	95% CI
Model 1	HT	0.439	0.133	0.001	1.552	1.195-2.015
	HR	0.946	0.072	< 0.001	2.576	2.238-2.964
Model 2	HT-HR	0.471	0.035	< 0.001	1.601	1.496-1.714

Note: Model 1 and Model 2 Age, Gender, Smoking, BMI, IR, TG, UA, DM;  $\beta$ -regression coefficient, SE-standard error, OR-odds ratio, CI-confidence interval; HT-hypertension, HR-heart rate, BMI-body mass index, IR- insulin resistance, TG-triglyceride, UA-uric acid, DM-diabetes.

The AUC in an ROC curve was calculated to evaluate the predictive performance of HT, HR and HT-HR for CAN. For the HT variable, the AUC was 0.596 (95% CI: 0.565-0.627,  $P < 0.001$ ), indicating that HT moderately predicted DHF

(Figure 4). Whereas for both the HR and HT-HR variables, the AUC was 0.719 (95% CI: 0.690-0.748,  $P < 0.001$ ) and 0.743 (95% CI: 0.715-0.770,  $P < 0.001$ ), respectively, suggesting that HR and HT-HR strongly predicted CAN (Figure 4). A cut-off point for HT-HR was set to 4 of 7, and the sensitivity and specificity of CAN were 65.10% and 68.90% (Youden index = 0.340, data not shown), respectively. The sensitivity and specificity of CAN were 84.20% and 50.70% (Youden index = 0.349, data not shown), respectively, when the cut-off point was set to 3 of 7.

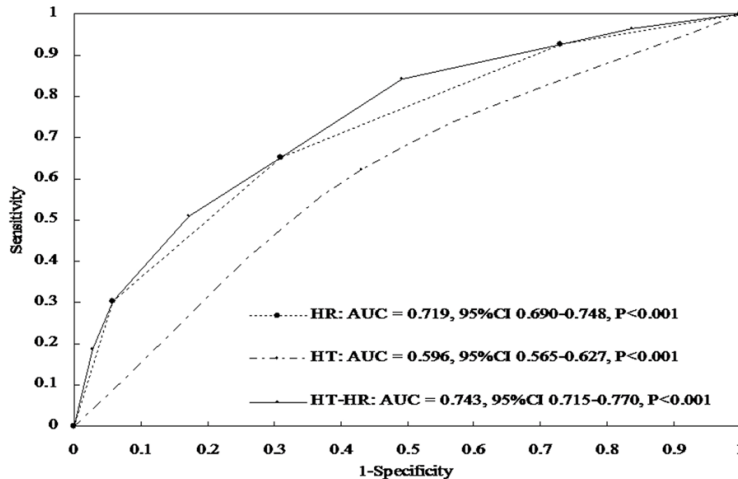
### Discussion

We conducted a large-scale population-based cross-sectional study to evaluate the extent to which HT and resting HR are associated with CAN among 2,092 participants in the Chinese population. This sample was a good representation of the Chinese population, and the findings may work similarly well outside the areas studied in China. More importantly, we first performed a predictive value analysis for CAN by using resting HR combined with HT. It is critical for us to understand the predictive value of HT and resting HR on CAN in the general population. This is partly because clinicians can expect to treat more HT patients having CAN progression. Moreover, a better understanding the predictive value of the two factors will help clinicians in preventing and treating CAN.

The main finding of the present study is that in the general population, HT and resting HR are strongly and independently associated with CAN. A higher CAN prevalence was found in subjects with HT as compared to subjects without HT ( $P < 0.001$ , Figure 1).

CAN prevalence increased with increased resting HR ( $P$  for trend  $< 0.001$ , Figure 2). CAN prevalence was 53.67% in subjects with resting HR  $> 85$  bpm, while its prevalence was 5.92% in subjects with resting HR  $< 65$  bpm. Univariate

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**Figure 4.** Receiver operating characteristic curves showed the performance of resting heart rate (HR), hypertension (HT) and categorical variable of HT-HR in predicting cardiovascular autonomic neuropathy (CAN) prevalence in this dataset. The 95% confidence interval (CI) is given in parentheses. AUC represents area under the curve. HR: AUC = 0.719, 95% CI 0.690-0.748,  $P < 0.001$ ; HT: AUC = 0.596, 95% CI 0.565-0.627,  $P < 0.001$ ; HT-HR: AUC = 0.743, 95% CI 0.715-0.770,  $P < 0.001$ .

analysis showed that HT and resting HR was very significantly associated with CAN ( $P < 0.001$  for both, **Table 2**), respectively. Moreover, MLR analysis after adjustment for potential confounding factors demonstrated that HT and resting HR very significantly and independently remain associated with CAN ( $P < 0.001$  for both, **Table 3**). These results provided strong evidence to support a good association of CAN with HT and resting HR. Our previous study [17] and other previous studies reported that HT is significantly associated with CA function indices. Wu et al. [14] conducted a study to explore the impact of CA function and IR on incident hypertension among 1638 subjects to indicate that CA dysfunction is an important predictor of incident HT independent of IR. Their previous study [13] indicated that altered CA function had already present in pre-hypertension or subjects with a family history of HT. Legrady et al. [15] provided evidence that HT played a role in development of CAN. A study performed by Liao et al. [21] to relate CA function measured by HRV with prevalent and incident HT at the population level, which examined a stratified random sample of 2,061 examinees from the biracial Atherosclerosis Risk in Communities cohort, suggested that cardiac autonomic function is associated with prevalent HT, and that reduced vagal function and the imbalance of

sympatho-vagal function are associated with the risk of developing HT. Interestingly, Celik et al. [16] performed a study to evaluate the relationship between inflammation and CA functions in hypertensive patients to reveal that there is an inflammatory process in hypertensive patients and inflammation is related with unbalanced CA functions. Studies have previously shown that resting HR is a critical factor and strong predictor of CAN in diabetic patients [11, 12]. Generally, increased resting HR was considered one of early indicators of CAN. For instance, van Dijk et al. [22] conducted a study to explore the effects of baseline BP and heart frequency on autonomic function tests to show that HR was correlated with CA imbalance.

Cardiovascular system is dually innervated, receiving fibers from the parasympathetic and sympathetic divisions of the autonomic nervous system. CAN manifests first in longer nerves. The vagus nerve, the longest of the autonomic nervous system, account for ~75% of all parasympathetic activity. The disease is ultimately the result of complex interactions among degree of glycemic control, disease duration, age-related neuronal attrition, and systolic and diastolic BP [23].

Another interesting finding was that resting HR alone and combined with HT had a high value in predicting CAN in the general population. As mentioned above, resting HR was very significantly and independently associated with CAN. The AUC was calculated to show that this factor strongly predicts CAN (AUC = 0.719, 95% CI: 0.690-0.748). For the analysis of the predictive value of HT alone on CAN, association analysis showed that HT was very significantly and independently associated with CAN, however, the AUC was calculated to indicate that HT moderately predicts CAN (AUC = 0.596, 95% CI 0.565-0.627,  $P < 0.001$ ). We used a categorical variable of HT-HR, which combined information between resting HR and HT, to signify a high value in predicting CAN in the general population (AUC = 0.743, 95% CI 0.715-0.770,  $P < 0.001$ ). The sensitivity and specificity of CAN

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were 84.20% and 50.70% when the optimal cut-off point of HT-HR was set to 3 of 7. In particular, the CAN prevalence was 59.02% in subjects with resting HR > 85 bpm and HT (HT-HR = 7), while its prevalence decreased to 4.76% in subjects with resting HR < 65 bpm without HT (HT-HR = 0). These results provide evidence that resting HR and HT-HR have a high value in predicting CAN in the general Chinese population. To our knowledge, this is the first study to have reported resting HR combined with HT having such a high predictive value for CAN in a Chinese population. This finding is of importance to the clinical practice of preventing and treating CAN in the general population. The categorical variable HT-HR combines information on HT and resting HR, but it cannot obtain a sensitivity of 100%. A false negative is mainly attributed to the fact that other risk factors contribute to the outcome. In this study, some of the patients with CAN were not obese, or had a normal resting HR due to both impaired sympathetic and parasympathetic nervous systems. Little is known about the CAN prevalence in subjects with a normal resting HR in the population. In addition, false-negative individuals had a lower resting HR, indicating that those people had long-term CAN. The exact mechanism underlying the association between CAN and HT or resting HR has not been fully elucidated. In the present study, we did not determine the mechanism by which TG modifies metabolic factors and induces DHF.

Several limitations of this study deserve comment. First, the study design was cross-sectional, and thus the temporal sequence between risk factors and outcome was questionable. In addition, it is important to mention that our study was performed on Chinese individuals, and our findings may not be relevant to people of other ethnicities.

In conclusion, a higher CAN prevalence was frequently found in subjects with increased resting HR and/or HT. There was a tendency toward increased CAN prevalence with increased resting HR. Our findings signify that resting HR and HT are independently associated with CAN and resting HR alone and combined with HT both have a high predictive value in predicting CAN in the general population.

### Acknowledgements

This work was supported by a grant from the Clinical Medicine Foundation of Shanghai

Tongji Hospital (Clinicaltrials.org Identifier Number: NCT02462616).

### Disclosure of conflict of interest

None.

### Authors' contribution

Jin Zhang Designed study, analyzed data and wrote manuscript; Fangfang Zeng Contributed reagents/materials/analysis tools; Zi-Hui Tang Contributed reagents/materials/analysis tools; Haiming Shi Conceived and designed study.

### Abbreviation

BMI, Body mass index; CI, Confidence intervals; CAN, Cardiovascular autonomic neuropathy; SCr, Serum Creatinine; DBP, Diastolic blood pressure; DM, Diabetes; FPG, Fasting plasma glucose; HbA1c, Glycosylated hemoglobin; HDL, High-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment insulin resistance estimate; HRV, Heart rate variability; HT, Hypertension; IDF, International Diabetes Federation; LDL, Low-density lipoprotein cholesterol; MetS, Metabolic syndrome; MLR, Multivariable logistic linear regression; OGTT, Oral glucose tolerance test; OR, Odds ratios; PBG, Postprandial blood glucose; HT, Hypertension; SBP, Systolic blood pressure; TC, Serum total cholesterol; TG, Triglyceride; WC, Waist circumference; UA, Uric acid.

**Address correspondence to:** Dr. Haiming Shi, Department of Cardiology, Fudan University Huashan Hospital, No. 12 Wulumuqi Road, Building 12#, Shanghai 200024, China. Fax: 0086-021-5228-8286; E-mail: shihaiminghuashan@163.com; Dr. Zihui Tang, Departments of Endocrinology and Metabolism, Shanghai Tongji Hospital, Tongji University School of Medicine, Room 1520#, Building 6#, No. 389 Xincun Road, Shanghai 200065, China. Fax: 0086-021-6428-8286; E-mail: albert.tang@163.com

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