High Pulse Pressure is a Risk Factor for Stroke in Elderly Individuals with Coronary Heart Disease and Diabetes Mellitus

Hao Wang[1,#], Tao Tao[1,#], Shan-Chun Zhang[2], Yu-Tao Guo[1], Yang Shi[1], Zhi-Bin Li[3] and Yu-Tang Wang[1,*]

[1]*First Geriatric Cardiology Division, Chinese PLA General Hospital, BeiJing, 100853, China*

[2]*Geriatric Neurology Division, Chinese PLA General Hospital, BeiJing, 100853, China*

[3]*Geriatric Endocrinology Division, Chinese PLA General Hospital, BeiJing, 100853, China*

Abstract: *Background*: The association between pulse pressure and the risk of stroke in elderly patients with multiple comorbidities is not well understood. The present study aimed to investigate the association between pulse pressure and the risk of stroke in elderly patients.

Measurements: We retrospectively assessed stroke/ transient ischemic attack (TIA) risk factors in 623 patients (33% female, median age, 74 years) with coronary heart disease (CHD) and diabetes mellitus (DM) at Chinese PLA General Hospital. The effects of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure on the risk of stroke/TIA were assessed using a binary logistic regression analysis. The ability of changes in blood pressure to predict the risk of stroke/TIA was assessed using a receiver operating characteristics curve.

Results: 228 (36.59%) patients had a stroke/TIA. DBP was significantly lower in the patients with stroke/TIA than in those without (75.83 ± 11.14 vs. 78.91 ± 11.85, P = 0.001). Pulse pressure was markedly higher in the stroke/TIA compared with the non-stroke/TIA group (61.34 ± 14.59 vs. 56.01 ± 14.65, P < 0.001). SBP was not significantly different between the groups. The multivariate analysis revealed pulse pressure (odds ratio, (OR), 1.02, 95% confidential interval (CI), 1.01–1.04, P < 0.001) and DBP ≤70 mmHg (OR, 95% CI, 1.44, 1.01–2.06, P=0.044) were independently associated with the risk of stroke/TIA. The *c*-statistics (95% CI) for pulse pressure and DBP ≤70 mmHg for predicting stroke/TIA were 0.62 (0.57–0.66; P<0.001) and 0.56 (0.51-0.61; P=0.006), respectively. A cutoff of 38 mmHg pulse pressure showed good predictive ability for the risk of stroke/TIA (sensitivity 97%, specificity 96%).

Conclusion: Low DBP and high pulse pressure, most likely the result of the low DBP, were risk factors for stroke/TIA in elderly patients with CHD and DM.

Keywords: Pulse pressure, Stroke, Elderly, Coronary heart disease, Diabetes mellitus.

BACKGROUND

Most elderly individuals experience multiple comorbidities and many are at high risk for stroke. For example, the prevalence of hypertension was 70%, coronary heart disease (CHD) was 20%, and diabetes mellitus (DM) was 27% among elderly people worldwide [1-4]. Hypertension, which is the most important known risk factor for stroke, is present in ~77% of patients with a first stroke, and has been estimated to cause ~54% of stroke cases worldwide [2]. Elderly patients with CHD and DM often have a high pulse pressure. However, the blood pressure profile of elderly patients with both CHD and DM has not been fully characterized, and the impact of blood pressue on the risk of stroke/ transient ischemic attack (TIA) in these patients is not known.

The present study investigated the blood pressure profile of elderly patients with CHD and DM. Furthermore, we assessed the impact of high pulse pressure and low diastolic blood pressure (DBP) on the risk of stroke.

METHODS

Subjects

We studied 623 elderly patients (age ≥60 years) with CHD and DM who were admitted to Chinese PLA General Hospital between January 2011 and December 2012. The study was approved by the Ethics Committee of the Chinese PLA General Hospital and performed in accordance with the principles of the Declaration of Helsinki. Inclusion criteria included patients aged 60 years or over, patients should suffered from CHD and DM simultaneously, and patients' electronic medical records should be complete. Exclusion criteria included recent febrile illness and inflammatory disease, active malignancy, concurrent use of steroids or other immunosuppressive agents, renal or liver failure, chronic heart failure, and atrial fibrillation.

*Address correspondence to this author at the First Geriatric Cardiology Division, Chinese PLA General Hospital, 28 Fuxing Rd, Beijing 100853, China; Tel: 86-10-66876221; Fax: 86-10-66876221; E-mail: wyt301@sina.com

[#]These authors are contributed equally to this manuscript.

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Definition of Terms

CHD was classified as stable angina, unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI). Stable angina was defined as at least a 3-month history of chronic, stable, effort-induced angina relieved by rest or nitroglycerin, together with laboratory test results and electrocardiography (ECG), computed tomography (CT) angiography, or coronary artery angiography results [5]. The UA and NSTEMI diagnoses were based on typical angina, typical ischemic changes in the ECG (new or transient depression of the ST-segment ≥0.1 mV, or T wave inversion of ≥0.2 mV), and detection of cardiac biomarkers [6]. STEMI was defined as typical dynamic changes in cardiac biomarkers plus at least one of the following criteria: 1) clinical symptoms of cardiac ischemia, 2) ECG changes associated with myocardial ischemia defined as new ST-segment change or left bundle-branch block, 3) a pathological Q wave on the ECG, or 4) new imaging evidence showing loss of myocardial vitality or segmental wall motion abnormalities [7]. DM was defined as fasting glucose ≥7.0 mmol/L, 2-h postprandial glucose ≥11.1 mmol/L, glycated hemoglobin (HbA1c) ≥6.5%, or receiving hypoglycemic medication [8]. Hypertension was defined as systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg, or receiving antihypertensive treatment [9]. Stroke was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist and verified by CT scan or magnetic resonance imaging (MRI).

Clinical Examination

The clinical examination consisted of a personal interview and physical examination. Height, weight, and waist circumference were measured with the patients wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Waist circumference was measured at the minimum circumference between the costal margin and iliac crest. Blood pressure was measured twice at 5-min intervals using a mercury sphygmomanometer. Korotkoff first and fifth phase sounds indicated SBP and DBP respectively, and blood pressure was defined as the average of the two measurements. Pulse pressure was defined as the difference between SBP and DBP. Blood samples were drawn from the antecubital vein after an 8-h fast to measure fasting blood glucose levels and HbA1C. Additionally, we measured 2-h postprandial blood glucose. Information regarding the physician's diagnosis of stroke/TIA, hypertension, high low-density lipoprotein cholesterol (LDL-c), high triglycerides (TG), high total cholesterol (TC), low high-density lipoprotein cholesterol (HDL-c), and past percutaneous coronary intervention (PCI) was collected. Furthermore, we collected information on concomitant therapies including nitrates, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, calcium antagonists, statins, aspirin, clopidogrel, and hypoglycemic agents.

Statistical Analysis

Continuous variables were expressed as means ± standard deviation (SD), and categorical variables were expressed as percentages. Differences in continuous and categorical variables were calculated using independent samples *t*-tests and the chi-square test, respectively. A binary logistic regression analysis was performed to identify potential risk factors for stroke/TIA. Receiver-operator characteristic (ROC) curve analyses were generated to test the predictive ability (expressed as a *c*-statistic) of pulse pressure/diastolic pressure for stroke. Confidence intervals (CI) were 95%. Entry was set at P <0.05 and retention at P <0.10. The Statistical Package for the Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA) was used to conduct the statistical tests, and *P*-values <0.05 were deemed to indicate statistical significance.

RESULTS

The study included 623 elderly patients (33% female; median age, 74 years). Of those, 228 (36.59%) had had a stroke/TIA and 467 (74.96%) had hypertension. The patients with stroke/TIA were prescribed ACEI/ARB, calcium antagonist, aspirin, clopidogrel and alpha-glucosidase inhibitors more frequently than those without stroke/TIA. The baseline characteristics of the study population are shown in Table **1**.

DBP was significantly lower in patients with stroke/TIA than in those without (75.83 ± 11.14 vs. 78.91 ± 11.85, respectively; P = 0.001), whereas pulse pressure was markedly higher in the stroke/TIA group than in the no-stroke/TIA group (61.34 ± 14.59 vs. 56.04 ± 14.65, respectively; P < 0.001). SBP was not significantly different between groups (Table **2**).

The multivariate analysis revealed that pulse pressure was independently associated with stroke/TIA

Table 1: Baseline Characteristics of Elderly Patients with Coronary Heart Disease and Diabetes Mellitus

	Overall cohort (n = 623)	Patients without stroke/TIA (n = 395)	Patients with stroke/TIA (n = 228)	P-value
Age, years (mean/SD)	74.01 ± 8.10	73.54 ± 8.08	74.81 ± 8.09	0.060
BMI, kg/m^2 (mean/SD)	25.07 ± 2.74	25.00 ± 2.70	25.18 ± 2.81	0.443
Waist circumference, cm (mean/SD)	88.64 ± 10.21	88.64 ± 10.33	88.62 ± 10.00	0.981
Medical history				
Hypertension	467 (74.96%)	293 (74.18%)	174 (76.32%)	0.820
Past PCI, n (%)	183 (29.37%)	118 (29.87%)	65 (28.50%)	0.784
High LDL, n (%)	248 (39.80%)	152 (38.48%)	96 (42.10%)	0.396
High TG, n (%)	76 (12.19%)	44 (11.13%)	32 (14.03%)	0.310
High TC, n (%)	193 (31.98%）	123 (31.14%)	70 (30.70%)	0.928
Low HDL, n (%)	255 (40.93%)	165 (41.77%)	90 (39.47%)	0.612
Fasting glucose, mmol/L (mean/SD)	7.31 ± 1.35	7.39 ± 1.78	7.17 ± 2.12	0.167
2-h post-prandial glucose, mmol/L (mean/SD)	10.82 ± 3.10	10.92 ± 2.81	10.67 ± 3.54	0.334
HbA1C, % (mean/SD)	7.26 ± 1.35	7.36 ± 1.35	7.07 ± 1.34	0.009
Concomitant therapy, n (%)				
Nitrates, n (%)	413 (66.29%)	263 (66.58%)	150 (65.78%)	0.861
ACEI, n (%)	212 (34.03%)	109 (27.59%)	103 (45.17%)	<0.001
ARB, n (%)	189 (30.34%)	106 (26.84%)	83 (36.40%)	0.015
β-blockers, n (%)	330 (52.97%)	214 (54.17%)	116 (50.88%)	0.454
Calcium antagonist, n (%)	294 (47.19%)	163 (41.26%)	131 (57.45%)	<0.001
Statin, n (%)	459 (73.67%)	285 (72.15%)	174 (76.32%)	0.299
Aspirin, n (%)	462 (74.20%)	267 (67.6%)	195 (85.5%)	<0.001
Clopidogrel, n (%)	178 (28.57%)	97 (24.56%)	81 (35.52%)	0.004
Insulin, n (%)	262 (42.05%)	157 (39.74%)	105 (46.05%)	0.130
Metformin, n (%)	276 (44.30%)	199 (50.37%)	77 (33.77%)	<0.001
Sulfonylureas, n (%)	173 (27.77%)	120 (30.38%)	53 (23.24%）	0.063
Glinides, n (%)	94 (15.09%)	62 (15.69%)	32 (14.04%)	0.643
Thiazolidinediones, n (%)	19 (3.05%)	11 (2.78%)	8 (3.50%)	0.634
Glucosidase inhibitor, n (%)	280 (44.94%)	164 (41.52%)	116 (50.88%)	0.024

BMI, body mass index; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. Data are presented as means (standard deviation), or absolute numbers (percentage). *P*-value, patients with stroke/TIA compared with those without stroke/TIA.

Table 2: Systolic Blood Pressure, Diastolic Blood Pressure, and Pulse Pressure in Elderly Patients with Coronary Heart Disease and Diabetes Mellitus (*n* = 623)

Blood pressure (mmHg)	Patients with stroke/TIA (*n* = 228)	Patients without stroke/TIA (*n* = 395)	*P*-value
SBP	137.18 ± 16.33	134.92 ± 16.14	0.096
DBP	75.83 ± 11.14	78.91 ± 11.85	0.001
Pulse pressure	61.34 ± 14.59	56.01 ± 14.65	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3: Binary Logistic Regression: Risk Factors for Stroke/TIA

Variable	OR	95% CI	*P*-value
Age	1.01	0.99–1.03	0.201
Sex	0.96	0.66–1.38	0.828
BMI	1.02	0.95–1.09	0.487
Waist circumference	0.99	0.97–1.01	0.738
HbA1C	0.88	0.76–1.01	0.088
Pulse pressure	1.02	1.01–1.04	<0.001
DBP ≤70 mmHg	1.44	1.01–2.06	0.044

BMI, body mass index; DBP, diastolic blood pressure; OR, odds ratio; CI, confidence interval.

Table 4: Predictive Value of Blood Pressure for Stroke/TIA According to the ROC Analysis

Blood pressure (mmHg)	AUC (*c*-statistic)	95% CI	*P*-value
SBP	0.53	0.48–0.57	0.193
DBP ≥ 90 mmHg	0.45	0.41–0.50	0.088
DBP≤70 mmHg	0.56	0.51–0.61	0.006
Pulse pressure	0.62	0.57–0.66	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; AUC, area under curve; CI, confidence interval; ROC, receiver-operator characteristic.

(odds ratio, (OR), 1.02, 95% CI, 1.01–1.04, *P* < 0.001). DBP ≤70 mmHg was an independent predictor of stroke/TIA after adjusting the age, sex, BMI, waist circumference, and HbA1C (OR, 95% CI, 1.44, 1.01–2.06, *P* = 0.044; Table **3**).

The *c*-statistics (95% CI) for pulse pressure and DBP ≤70 mmHg for predicting stroke/TIA were 0.62 (0.57–0.66; *P* < 0.001) and 0.56 (0.51–0.61; *P* = 0.006), respectively. The optimal pulse pressure cutoff was 38 mmHg (sensitivity 97%, specificity 96%; Table **4**).

DISCUSSION

Our main finding was that elderly patients with CHD and DM had high pulse pressure, likely caused by a decrease in DBP. Moreover, elevated pulse pressure ≥38 mmHg and low DBP ≤70 mmHg were independent predictors of the risk of stroke/TIA in our subjects.

We found that elderly patients with CHD and DM frequently had hypertension (75%); however, SBP was not significantly different between patients with and without stroke/TIA. In contrast, pulse pressure was significantly higher in patients with stroke/TIA than in those without, which may have been the result of the low DBP. These findings suggest that CHD and DM contribute to the progression of atherosclerosis independent of the pathophysiology of hypertension.

Our result revealed that pulse pressure at or above 38 mmHg was a potential predictor of the risk of stroke/TIA in elderly patients with CHD and DM. Several previous studies have found an association between high pulse pressure and the risk of stroke. Zheng *et al*. conducted a cross-sectional study of 6,104 patients ≥35 years of age with uncontrolled hypertension and found that pulse pressure was associated with ischemic stroke (OR 1.479, 95% CI, 1.373–2.914) [10]. The Systolic Hypertension in the Elderly Program (SHEP) studied 4,632 elderly patients with isolated systolic hypertension. In the active treatment group, a 10-mmHg increase in pulse pressure was associated with a 24% increase in the risk of stroke after controlling for SBP and other known factors, and a 20% increase in the risk of stroke after controlling for DBP and other known factors during a 5-year follow-up [11]. Furthermore, a meta-analysis of seven randomized clinical trials found that an increase in pulse pressure was significantly associated with fatal stroke at an advanced age [12], suggesting that pulse pressure is a risk factor for stroke in elderly patients.

We found that DBP ≤70 mmHg was an independent risk factor for stroke/TIA. DBP was more likely than SBP to be associated with the risk of stroke in elderly patients with atherosclerosis. Previous studies have shown that low DBP was associated with an increase in adverse cardiovascular events [13]. In the active treatment group of the SHEP study, the protective effect of medication was observed only among subjects whose DBP did not decrease to or below 55 mmHg [11]. Moreover, a previous study showed that pulse pressure was significantly associated with increased cardiovascular events only when DBP was <90 mmHg in a cohort with heart failure, regardless of SBP level [14].

Furthermore, CHD itself may be involved in the development of high pulse pressure and low DBP. Previous studies have confirmed an association between high pulse pressure and adverse cardiovascular events such as coronary ischemia [15, 16]. This may reflect an underlying association between atherosclerosis and pulse pressure. A prospective cohort of 19,083 French males initially aged between 40 and 69 years found that increased pulse pressure was a predictor of all-cause, cardiovascular, and CHD mortality during an average follow-up of 19.5 years [17]. The International Verapamil SR-Trandolapril Study (INVEST), a randomized trial of 22,576 patients with CHD and hypertension, found that pulse pressure was a predictor of non-fatal stroke, non-fatal myocardial infarction, and death (all-cause) and was independent of SBP, DBP, and mean arterial pressure [18]. The SHEP study showed that increased pulse pressure at baseline was associated with stroke and total mortality independent of mean blood pressure in elderly subjects with isolated systolic hypertension [19]. Furthermore, a prospective study of 2,207 patients with hypertension found that high pretreatment pulse pressure (≥63 mmHg) was associated with an increased risk of myocardial infarction and stroke during a mean follow-up of 5 years [20]. In a study of 2,152 individuals aged ≥65 years and without congestive heart failure at baseline, a 10-mmHg increment in pulse pressure was associated with a 12% increase in the risk of CHD, a 14% increase in the risk of congestive heart failure, and a 6% increase in overall mortality during a 10-year follow-up [18].

DM has been well acknowledged as an important risk factors for cardiovascular disease and now been accepted as CHD risk equivalents. Studies have demonstrated that individuals diagnosed with DM have a 2-4 fold higher risk of CHD [21]. Moreover, there are crosstalk between DM and CHD. The cardiovascular disease accounts for more than 50% of the deaths in patients with DM [22]. Even family history of DM has been shown to increase the risk of CHD. Pannaciulli *et al*. [23] have demonstrated that intima-media thickness of the common carotid artery, which has been considered as a powerful marker of coronary atherosclerosis, was significantly associated with family history of DM. Individuals with DM were also found to be in poor control of blood pressure and have excess morbidity and mortality related to stroke [24]. When patients suffer from CHD and DM simultaneously, no doubly, the control of blood pressure in this population should raise more concerns. It has been postulated that hyperinsulinemia, hyperlipidimia, arterial stiffness and accumulation of extracellular fluids all play an important role in the development of hypertension in patients with DM. A study has found that, in patients with DM, DBP at 70-74 mmHg and lower than 70 mm Hg was associated with increased risk (HR1.89;1.40 to 2.56, P<0.001)for all cause mortality when compared with patients who received usual control of DBP (80-84 mm Hg) (HR 1.32; 1.02 to 1.78, P=0.04) [25]. This finding was resembled with our results that low DBP ≤70 mmHg were independent predictors of the risk of stroke/TIA in patients with CHD and DM.

The widening of pulse pressure has been proved to be the result of increasing of SBP and declining of DBP as aging. When patients reaching sixth decade, pulse pressure is found to be the key blood pressure measure in the elderly and increase in importance as a risk factor for stroke and death [26]. As far as sex is concerned, stroke occurs more commonly than CHD in women. When reaching older ages, women with hypertension significantly outnumber men with hypertension [27]. The incidence of stroke tends to increase as aging .Women have longer life expectancy than men [28]. This could explain the fact that women account for 60% all stroke events. But, in our study, age (OR 1.01, 95%CI 0.99-1.03, p=0.201) and sex (OR 0.96, 95%CI 0.66-1.38, p=0.828) were not associated with the risk of stroke/TIA. This could be attributed to the relatively small number of subjects in our present study.

The present study had several limitations. First, the data of the type of stroke was not available. Thus, the influence of pulse pressure on ischemic/hemorrhagic stroke could not be analyzed retrospectively. Second, our study was of a cross-sectional design, and the predictive value of pulse pressure and DBP should be confirmed in large-sample cohort study.

CONCLUSIONS

In conclusion, low DBP and pulse pressure (38 mmHg), which may be the result of low DBP (≤70 mmHg), were more strongly associated with the risk of stroke/TIA in elderly patients with CHD and diabetes mellitus than SBP.

ABBREVIATIONS

ACEI = Angiotensin converting enzyme inhibitors

ARB = angiotensin receptor blockers

BMI = Body mass index

CHD = Coronary heart disease

CI = Confidence intervals

CT = Computed tomography

DBP = Diastolic blood pressure

DM = Diabetes mellitus

ECG = Electrocardiography

HbA1c = glycated hemoglobin

HDL-c = high-density lipoprotein cholesterol

HR = Hazard ratio

INVEST = The International Verapamil SR-Trandolapril Study

LDL-c = Low-density lipoprotein cholesterol

MRI = Magnetic resonance imaging

NSTEMI = Non-ST elevation myocardial infarction

PCI = Percutaneous coronary intervention

ROC = Receiver-operator characteristic

SBP = Systolic blood pressure

Syst-Eur = The Systolic Hypertension in Europe trial

SHEP = The Systolic Hypertension in the Elderly Program

SD = Standard deviation

STEMI = ST elevation myocardial infarction

TC = Total cholesterol

TG = Triglycerides

TIA = Transient ischemic attack

UA = Unstable angina

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

Hao Wang, Yu-Tang Wang, and Yu-Tao Guo: Study design. Hao Wang, Tao Tao, Zhi-Bin Li, and Shan-Chun Zhang : Acquisition of participants and data. Hao Wang, Yang Shi and Tao Tao: Analysis and interpretation of data. Hao Wang, Tao Tao, and Shan-Chun Zhang: Preparation of manuscript. Hao Wang, and Tao Tao contributed equally to this manuscript. All the authors have read and approved the final manuscript.

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