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Association of central blood pressure and cardiovascular diseases in diabetic patients with hypertension

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Abstract

To evaluate association of central blood pressure (BP) and cardiovascular disease (CVD) in diabetic patients with hypertension.

This was a cross-section study and 360 participants were enrolled. Baseline characteristics were collected and indices of central BP including central systolic/diastolic BP (SBP/DBP), augmentation index adjusted for 75 beats per minute of heart rate (AIx@75) were measured. Participants were separated into with and without CVD groups and between-group differences were assessed. Linear regression analysis was used to evaluate potential risk factors for increased AIx@75. Logistic regression analysis was used to evaluate association between central SBP and AIx@75 with CVD.

Mean age was 50.6 years and male participants accounted for 57.8%. Thirty-five and 43 participants had coronary heart disease and ischemic stroke. Compared with participants without CVD, those with CVD were more likely to be male and smokers and had higher glycated hemoglobin level. Additionally, participants with CVD had significantly higher central SBP and AIx@75 compared with those without CVD. Ageing, male gender, and presence of coronary heart disease and ischemic stroke were associated with increased AIx@75, whereas renin–angiotensin–axis inhibitor was associated with reduced AIx@75. After adjusted for traditional risk factors including brachial SBP, both central SBP, and AIx@75 remained significantly associated with CVD, with odds ratio and 95% confidence interval of 1.09 (1.08–1.31) and 1.20 (1.15–1.42), respectively.

Diabetic patients with hypertension, ageing, male gender, and presence of CVD are independent risk factors of central BP increase; and increased central SBP and AIx@75 are significantly associated with CVD.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AIx@75 = augmentation index adjusted for 75 beats per minute of heart rate, ARB = angiotensin receptor blocker, BMI = body mass index, BP = blood pressure, CVD = cardiovascular disease, DM = diabetes mellitus, SBP/DBP = systolic/diastolic BP.

Keywords: cardiovascular disease, central blood pressure, diabetes mellitus, hypertension

1. Introduction

Hypertension is a major risk factor for cardiovascular diseases (CVD) and all-cause mortality.[1–3] Numerous randomized controlled trials using antihypertensive drugs and meta-analysis demonstrate that lowering peripheral blood pressure (BP) is beneficial for reducing cardiovascular and renal events.[4–6] In recent decades, some observational studies suggest that peripheral BP measured by brachial artery may not necessarily represent BP measured in the aortic artery which is known as central BP.[7,8] In addition, some clinical trials also revealed that despite with comparable peripheral BP, patients with high central BP had significantly higher cardiovascular risk compared with those with low central BP,[7,9,10] indicating that central BP might be an independent predictor for CVD.[11,12]

Diabetes mellitus (DM) is another significant risk factor for cardiovascular and renal diseases.[13] Numerous epidemiological studies demonstrate that DM is commonly accompanied with hypertension and patients with diabetes and hypertension have higher renal and cardiovascular risks compared with those with either hypertension or diabetes.[14,15] Therefore, better evaluating and managing BP in diabetic patients with hypertension is clinically relevant.

Up till now, few studies have specifically investigated the prognostic significance of central BP in Chinese populations with diabetes and hypertension. Therefore, our current study used a cross-sectional design to evaluate the association of central BP and prevalence of CVD in these populations; in addition, the potential risk factors for increased central BP would also be explored.

2. Methods

2.1. Studied participants

Studied participants were provided informed consent before recruitment and current study was approved by the Clinical and

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Experimental Research Ethic Committee of the Affiliated Hospital of Taishan Medical College, and all the performances were done in accordance with the Declaration of Helsinki. Included criteria were as follows: 18 to 75 years old; documented type 2 DM and essential hypertension. Excluded criteria were as follows: documented rheumatic diseases such as systemic lupus erythematosus had congestive heart failure, myocardial infarction, or cerebrovascular disease in the past 6 months.

2.2. Data collection

Demographic data such as age, gender, cigarette smoking status, duration of diabetes and hypertension, previous medical history, and current medications usage were collected using structured questionnaire. Anthropometric data such as height, body weight, and peripheral BP and heart rate at rest were measured by 2 investigators. Body mass index (BMI) was calculated by body weight in kilograms divided by height in squared meters. In brief, peripheral BP measured was based on the JNC7 guideline recommendation.[16] Patients sit quietly for 10 minutes with their back supporting. Nondominant arm was placed on the heart level and 3 BP readings were obtained with 1 minute interval between each reading, and the last 2 readings were used to calculate the mean brachial BP level. Coronary heart disease diagnosis was based on computer tomography coronary artery with contrast or coronary artery angiography, and ischemic stroke was based on clinical symptoms and computer tomography evidence, and composite CVD was comprised of coronary heart disease and ischemic stroke.

2.3. Central BP measurements

Central BP were measured using applanation tonometry with SphygmoCor device (AtCor medical) which used radial pulse and a validated generalized transfer function to estimate central BP from the peripheral signal. Before central BP measurement, participants were fasting for at least 8 hours and no medications were used at the same morning. Participants were put in a supine position for 10 minutes and all the procedures were performed based on previous description.[10] Central systolic and diastolic BP (SBP/DBP) and augmentation index adjusted for 75 beats per minute of heart rate (AIx@75) were derived for analysis.

2.4. Biochemical indices

After central BP measurement, fasting venous blood was drawn for lipid profiles, fasting plasma glucose and glycated hemoglobin, and serum creatinine and C-reactive protein levels evaluation.

2.5. Statistical analysis

Continuous variables were presented as mean ± SD and categorical variables were presented as number and percentages of cases. Continuous variables comparison was performed using Student *t* test and categorical variables comparison was performed using χ^2 or Fisher exact test. Participants were divided into with and without composite CVD groups and between-group differences were evaluated. In brief, coronary heart disease and ischemic stroke were combined as composite CVD. Linear regression analysis was used to evaluate the potential risk factors for increased AIx@75. Logistic regression analysis was used to evaluation the association between per 1-SD standardized increase of central SBP and AIx@75 with prevalence of composite CVD. Statistical analyses were computed using SPSS 17.0 (SPSS Inc, Chicago, IL). All the statistical tests were 2-sided and considered statistically significant when $P < .05$.

Table 1

General characteristics.

Variables	Value
Age, y	50.6 ± 11.7
Male, n, %	208 (57.8)
Smoking, n, %	125 (34.7)
Duration of HTN, y	6.6 ± 3.2
Duration of DM, y	5.2 ± 2.7
Weight, kg	57.8 ± 13.6
Height, m	1.65 ± 0.14
BMI, kg/m^2	23.4 ± 3.7
Brachial SBP, mm Hg	136 ± 22
Brachial DBP, mm Hg	77 ± 14
HR, bpm	75 ± 16
TC, mmol/L	5.0 ± 1.3
TG, mmol/L	1.8 ± 0.7
LDL-C, mmol/L	3.2 ± 1.1
HDL-C, mmol/L	1.2 ± 0.4
FPG, mmol/L	6.0 ± 1.4
HbA1c, %	6.7 ± 0.8
Cr, umol/L	80.6 ± 21.7
C-reactive protein, mg/L	8.3 ± 5.2
Central SBP, mm Hg	117 ± 13
Central DBP, mm Hg	76 ± 15
AIx@75, %	23.4 ± 12.5
CHD, n, %	35 (9.7)
IS, n, %	43 (11.9)
Composite CVD, n, %	78 (21.7)
ACEI/ARB, n, %	306 (85)
CCB, n, %	124 (34.4)
Beta-blocker, n, %	109 (30.3)
Diuretic, n, %	85 (23.6)
Statins, n, %	168 (46.7)
Aspirin, n, %	235 (65.3)
Sulfonylureas, n, %	116 (32.2)
Metformin, n, %	311 (86.4)
Glucosidase inhibitor, n, %	148 (41.1)
Thiazolidinedione, n, %	43 (11.9)
Insulin, n, %	113 (31.4)

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, AIx@75 = augmentation index at 75 heart rate, BMI = body mass index, CCB = calcium channel blocker, CHD = coronary heart disease, Composite CVD = composite cardiovascular diseases, Cr = creatinine, DBP = diastolic blood pressure, DM = diabetes mellitus, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HR = heart rate, HTN = hypertension, IS = ischemic stroke, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

3. Results

3.1. General characteristics

From September of 2015 to December of 2016, a total of 360 participants were enrolled and general characteristics were presented in Table 1. Mean age was 50.6 years and male participants accounted for 57.8%. Durations of hypertension and diabetes were 6.6 ± 3.2 and 5.2 ± 2.7 years, respectively. Notably, brachial SBP was higher than that in central SBP, while DBP was comparable between brachial and aortic artery, and mean AIx@75 was 23.4%. Thirty-five and 43 participants had coronary heart disease and ischemic stroke, respectively. The most commonly used antihypertensive and hypoglycemic drugs were renin–angiotensin–axis inhibitor (85%) and metformin (86.4%), respectively.

Table 2

Comparison between participants with and without composite CVD.

Variables	Without composite CVD (n = 282)	Composite CVD (n = 78)
Age, y	48.9 ± 10.3	51.5 ± 12.5
Male, n, %	159 (56.4)	49 (62.8)*
Smoking, n, %	92 (32.6)	33 (42.3)*
Duration of HTN, y	6.3 ± 2.7	6.7 ± 3.0
Duration of DM, y	5.0 ± 2.2	5.3 ± 2.9
Weight, kg	58.4 ± 13.2	57.1 ± 13.7
Height, m	1.66 ± 0.16	1.65 ± 0.12
BMI, kg/m^2	23.8 ± 3.5	23.1 ± 3.2
Brachial SBP, mm Hg	134 ± 20	137 ± 24
Brachial DBP, mm Hg	75 ± 12	76 ± 14
HR, bpm	75 ± 13	79 ± 16*
TC, mmol/L	4.8 ± 1.1	5.2 ± 1.4
TG, mmol/L	1.7 ± 0.8	1.8 ± 0.6
LDL-C, mmol/L	3.0 ± 0.9	3.3 ± 1.2
HDL-C, mmol/L	1.2 ± 0.3	1.1 ± 0.4
FPG, mmol/L	6.0 ± 1.3	6.1 ± 1.5
HbA1c, %	6.5 ± 0.7	6.8 ± 0.9*
C-reactive protein, mg/L	6.1 ± 3.4	10.5 ± 4.6*
Cr, umol/L	79.4 ± 20.3	82.2 ± 23.6
Central SBP, mm Hg	111 ± 10	119 ± 15*
Central DBP, mm Hg	75 ± 13	76 ± 15
AIx@75, %	21.3 ± 10.9	25.6 ± 13.7*
ACEI/ARB, n, %	239 (84.8)	67 (85.9)
CCB, n, %	98 (34.8)	26 (33.3)
Beta-blocker, n, %	84 (29.8)	25 (32.1)
Diuretic, n, %	68 (24.1)	17 (21.8)
Statins, n, %	130 (46.1)	38 (48.7)
Aspirin, n, %	182 (64.5)	53 (67.9)
Sulfonylureas, n, %	91 (32.3)	25 (32.1)
Metformin, n, %	242 (85.8)	69 (88.5)
Glucosidase inhibitor, n, %	116 (41.1)	32 (41)
Thiazolidinedione, n, %	33 (11.7)	10 (12.8)
Insulin, n, %	89 (31.6)	24 (30.8)

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, AIx@75 = augmentation index at 75 heart rate, BMI = body mass index, bpm = beat per minute TC = total cholesterol, CCB = calcium channel blocker, CHD = coronary heart disease, composite CVD = composite cardiovascular diseases, Cr = creatinine, DBP = diastolic blood pressure, DM = diabetes mellitus, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HR = heart rate, HTN = hypertension, IS = ischemic stroke, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TG = triglyceride.

* $P < .05$ versus without composite CVD group.

3.2. Comparisons between participants with and without composite CVD

Between-group differences were evaluated and as presented in Table 2, compared with participants without composite CVD, those with composite CVD were more likely to be male and smokers and had higher glycated hemoglobin level. No significant between-group differences in hypertension and diabetes duration, medications usage, lipid profiles, and brachial SBP and DBP were observed. Nevertheless, participants with composite CVD had significantly higher central SBP and AIx@75 compared with those without composite CVD.

3.3. Risk factors for increased AIx@75

Linear regression analysis was performed to evaluate potential risk factors for increased AIx@75. As presented in Table 3, overall, in the multivariate regression analysis model, ageing, male gender, and presence of coronary heart disease and ischemic stroke were associated with increased AIx@75, whereas usage of renin–angiotensin–axis inhibitor was associated with reduced AIx@75.

Table 3

Linear regression analysis.

Factors	Univariate	Multivariate
Age, y	1.36 (1.12–1.69)	1.19 (1.06–1.33)
Male	1.20 (1.08–1.43)	1.07 (1.02–1.15)
Smoking	1.06 (1.01–1.25)	1.00 (0.95–1.08)
BMI, kg/m^2	1.09 (1.02–1.17)	0.98 (0.92–1.04)
HR, bpm	0.94 (0.89–1.03)	NS
HbA1c, %	1.25 (1.14–1.42)	1.11 (0.99–1.20)
C-reactive protein	1.17 (1.09–1.30)	1.06 (0.96–1.15)
ACEI/ARB	0.90 (0.85–0.97)	0.94 (0.88–0.98)
CCB	0.96 (0.91–1.02)	NS
Beta-blocker	1.04 (0.98–1.11)	NS
Diuretic	1.01 (0.94–1.08)	NS
Statins	0.97 (0.93–1.18)	NS
Aspirin	1.05 (0.86–1.24)	NS
Sulfonylureas	0.95 (0.90–1.07)	NS
Metformin	0.92 (0.84–1.02)	NS
Glucosidase inhibitor	1.01 (0.93–1.06)	NS
Thiazolidinedione	0.98 (0.91–1.04)	NS
Insulin	1.04 (0.99–1.10)	NS
CHD	1.18 (1.06–1.33)	1.12 (1.03–1.29)
IS	1.09 (01.02–1.20)	1.04 (1.01–1.13)

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BMI = body mass index, bpm = beat per minute, CCB = calcium channel blocker, CHD = coronary heart disease, HbA1c = glycated hemoglobin, HR = heart rate, IS = ischemic stroke, NS = nonsignificant.

3.4. Association between central SBP and AIx@75 with composite CVD

As presented in Table 4, association between central SBP and AIx@75 with composite CVD was evaluated with a stepwise adjusted model. Overall, in model 3, after adjusted for age, male gender, smoking, body mass index, glycated hemoglobin, total cholesterol, renin–angiotensin–axis inhibitor, and brachial SBP, both central SBP and AIx@75 remained significantly associated with the prevalence of composite CVD, with odds ratio and 95% confidence interval of 1.09 (1.08–1.31) and 1.20 (1.15–1.42), respectively.

4. Discussion

Diabetic patients with concurrent hypertension are at higher cardiovascular risks than their counterparts without hypertension. Therefore, better evaluation of BP in these specific populations is clinically relevant. Our present study suggests that with comparable brachial BPs, diabetic hypertensive patients with CVD have significantly higher central SBP and AIx@75 compared with their counterparts without CVD; and increased central SBP and AIx@75 are significantly associated with higher prevalence of composite CVD. Ageing, male gender, and presence of CVD are major risk factors for increased AIx@75 whereas renin–angiotensin–axis inhibitor appears to reduce AIx@75, suggesting that angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) may have favorable effects on reducing central BP compared with other classes of antihypertensive drugs.

Table 4

Logistic regression analysis.

	Unadjusted	Model 1	Model 2	Model 3
Central SBP, mm Hg	1.69 (1.45–1.87)	1.42 (1.23–1.70)	1.30 (1.20–1.54)	1.09 (1.08–1.31)
AIx@75, %	1.82 (1.61–2.03)	1.71 (1.54–1.93)	1.56 (1.42–1.77)	1.20 (1.15–1.42)

Model 1, adjusted for age and male gender; Model 2, further adjusted for smoking, body mass index, glycated hemoglobin and total cholesterol; Model 3, further adjusted for ACEI/ARB and brachial systolic blood pressure.

It is well known that both diabetes and hypertension are major health problems around the world.[17] Previous some clinical trials indicate that brachial SBP lower than 130 mm Hg is beneficial for reducing cardiovascular events in diabetic patients.[18,19] However, the ACCORD trial suggests that there is no solid additional cardiovascular benefit in patients with brachial SBP $\leq$ 120 mm Hg versus SBP $\leq$ 140 mm Hg.[20] The underlying mechanisms are multifactorial. One might speculate that brachial BP might not necessarily represent hemodynamic change in aortic artery. Indeed, prior numerous clinical studies reveal that central BP is superior to brachial BP in relation to CVD. For example, in the Strong Heart Study,[7] Roman et al demonstrated that compared with brachial BP, central BP was more strongly related to vascular hypertrophy, extent of atherosclerosis, and cardiovascular events. In another post-hoc analysis of clinical trial (the ASCOT),[10] Williams et al found that despite comparable achievement of brachial BP, those with higher central BP experienced higher cardiovascular events, strongly suggesting that central BP might be an independent predictor of clinical outcomes. Consistent with previous findings,[7,10,21,22] our present study also suggested that despite comparable brachial BP between participants with and without composite CVD, those with composite CVD had significantly higher central SBP and AIx@75; logistic regression analysis further corroborated that both central SBP and AIx@75 were independent risk factors for CVD. Future prospective studies are warranted to investigate whether reduction of central BP could be favorable to reduce cardiovascular events.

Interestingly and importantly, linear regression analysis suggested that only renin–angiotensin–axis inhibitor was significantly associated with reduced central SBP and AIx@75. Indeed, several previous studies have shown that ACEI or ARB had better efficacies than diuretic or beta-blocker in reducing central BP.[23,24] Presumably, endothelial dysfunction and vascular fibrosis related to diabetes might render ACEI or ARB to be a preferred drug to improve aortic stiffness and reduce central BP.[25,26] In addition, we also observed that presence of coronary heart disease and ischemic stroke were another 2 independent risk factors for increased AIx@75, suggesting that presence of CVD might increase central BP. Presumably, patients with ischemic diseases might have more severe endothelial dysfunction, systemic inflammation, and higher sympathetic output,[27,28] which together increased central BP.

Several limitations of our current study needed to be addressed. First, cross-sectional design could not allow us to draw causal relationship. However, our study first revealed the association of increased central SBP and AIx@75 with CVD. Second, although several longitudinal studies have indicated the association of increased central BP and incident cardiovascular diseases, reverse causality in terms of presence of CVD contributed to central BP increase might be possible. Third, the findings of the current study could not be generalized to nondiabetic or normotensive populations. Fourth, the current study lacked the data on microalbuminuria which could reflect the pathological alterations of renal function and structure. In the future prospective cohort study, it is clinically relevant to monitor microalbuminuria change in these populations. Finally, medications usage might underestimate the association of central BP and prevalence of CVD.

5. Conclusion

In summary, in diabetic patients with hypertension, ageing, male gender, and presence of CVD are independent risk factors of central BP elevation. Increased central SBP and AIx@75 are significantly associated with composite CVD. In these specific populations, measurement of central BP may provide more valuable information for cardiovascular risk stratification.

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