Relationship and associated mechanisms between ambulatory blood pressure and clinic blood pressure with prevalent cardiovascular disease in diabetic hypertensive patients

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Abstract
The present study was to compare the association between ambulatory blood pressure (ABP) and clinic BP (CBP) with prevalent cardiovascular diseases (CVD); and the underlying mechanism would also be investigated concurrently.

Diabetic hypertensive patients were enrolled and divided into 2 groups based on presence of CVD. Twenty-four hour-ABP monitoring was performed and between-group differences were evaluated and logistic regression analysis was conducted.

A total of 568 diabetic hypertensive patients were enrolled, and the mean age was 60.8 years, male accounted for 67.8%. Mean durations of diabetes mellitus and hypertension were 6.1 ± 2.7 and 5.4 ± 3.3 years, respectively, and 20.6% had prevalent CVD. Compared to patients without CVD, patients with CVD had significantly higher body mass index (BMI), plasma aldosterone concentration (PAC), and serum sodium level. No significant between-group differences in CBP were observed. However, 24 hour-SBP, daytime-SBP and nighttime-SBP were all significantly higher in patients with CVD compared to those without CVD. Pearson correlation analysis showed that BMI was positively correlated with PAC and serum sodium level. Logistic regression analyses showed that the association between clinic SBP and DBP with CVD were progressively attenuated to nonsignificant. In contrast, both ambulatory SBP and DBP were independently associated with CVD. However, after being further adjusted for PAC, no significant association was observed between ambulatory SBP and CVD.

In diabetic hypertensive patients, ABP is superior to CBP in relation to CVD. The association between ambulatory SBP and CVD may be dependent on aldosterone excess.

Abbreviations: ABP = ambulatory blood pressure, ABPM = ambulatory blood pressure monitoring, ALT = alanine aminotransferase, BMI = body mass index, BP = blood pressure, CBP = clinic BP, Cr = creatinine, CVD = cardiovascular diseases, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, PAC = plasma aldosterone concentration, SBP = systolic BP, TC = total cholesterol, TG = triglyceride.

Keywords: aldosterone, ambulatory blood pressure, cardiovascular disease, clinic blood pressure, relationship

1. Introduction
Diabetes mellitus is a major public health problem around the world owing to its causal relationship with a variety of micro- and macro-vascular diseases.\(^1\)\(^,\)\(^2\) In the recent decades, several cross-sectional studies and longitudinal cohort studies have consistently showed that patients with diabetes mellitus have a higher incidence and prevalence of hypertension than those without diabetes mellitus.\(^1\)\(^,\)\(^3\) Furthermore, diabetic patients with hypertension are at increased risk of experiencing cardiovascular events than their diabetic counterparts without hypertension.\(^1\)\(^,\)\(^3\)\(^-\)\(^4\)

Therefore, previous guidelines recommended that in diabetic patients with hypertension, blood pressure (BP) level should be reduced to lower than 130/80 mm Hg.\(^5\) Indeed, in the past few years, several high-quality meta-analyses have shown that systolic BP (SBP) level lower than 130 mm Hg was associated with lower cardiovascular events.\(^6\)\(^,\)\(^7\) Despite the ACCORD-BP trial showed no statistical significant differences in the composite cardiovascular outcomes between the intensive (SBP < 120 mm Hg) and the standard BP (SBP < 140 mm Hg) groups.\(^8\) Ambulatory blood pressure monitoring (ABPM) has been recognized as a more accurate and comprehensive BP measurement modality compared to the clinic BP (CBP).\(^9\) ABPM could provide data on 24 hours, daytime, and nighttime BP as well as data on BP patterns.\(^9\) Previously, several studies have shown that in the general population, BP values obtained from ABPM were more closely associated with cardiovascular diseases (CVD) than that from CBP.\(^10\)\(^-\)\(^14\) Similarly, some observational studies also have shown that ambulatory blood pressure (ABP) was superior to CBP in relation to CVD in diabetic populations.\(^1\)\(^3\)\(^-\)\(^15\)

Aldosterone excess was positively associated with body mass index (BMI) in hypertensive patients.\(^16\) Diabetic patients commonly have a higher prevalence of central obesity and higher BMI than the general populations.\(^1\)\(^7\) We thus hypothesized that aldosterone excess might be the potential mechanisms in relation to CVD in diabetic hypertensive patients. In our
present study, we were going to evaluate the following aspects. On the one hand, we would compare whether ABP was superior to CBP in relation to prevalent CVD in our Chinese diabetic hypertensive patients. On the other hand, we would evaluate whether this association was dependent on aldosterone excess.

2. Methods

2.1. Studied populations

Studied populations were enrolled in the Third People’s Hospital of Huizhou from January of 2015 to August of 2016. The present study was approved by the Clinical Research Ethical Committee of the Third People’s Hospital of Huizhou and informed consent was obtained from each participant. Inclusion criteria were documented diabetes mellitus and hypertension; and exclusion criteria were those with type 1 diabetes mellitus, secondary hypertension, severe renal dysfunction with estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m², currently using aldosterone antagonist, or history of atrial fibrillation.

2.2. Demographic and anthropometric data

A constructed questionnaire was used to collect participant’s demographic data including age, gender, cigarette smoking status, duration of diabetes and hypertension, prevalent CVD, and present medication usage. Briefly, prevalent CVD included coronary heart diseases based on computer tomography with contrast or coronary angiography and ischemic stroke based on computer tomography and typical clinical symptoms, and transient ischemic attack was excluded. The height and weight were measured by investigators, which were used to calculate the BMI (weight in kilograms divided by height in square meters).

2.3. Biochemical parameters

Biochemical parameters including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), alanine aminotransferase (ALT), serum creatinine (Cr), sodium and potassium levels, and plasma aldosterone concentration (PAC) were evaluated using fasting venous blood.

2.4. BP measurements

Briefly, CBP measurements were conducted in accordance to the JNC-7 guideline recommendation. Patients sit quietly for 5 minutes with their back supported before BP measurement. Nondominant arm was selected and was placed on the desk, which was parallel to the level of heart. Appropriate cuff size was used, which could circle at least 80% perimeter of the arm. Three times measurements were performed with 1 minute interval and the last 2 BP readings were recorded and averaged for the CBP value. ABPM was subsequently conducted using model 90207 (Space-Labs Medical Inc., Redmond, WA). Nondominant arm was selected and BP measurements were set at every 20 minutes during daytime (6:00–22:00) and every 30 minutes during nighttime (22:00–6:00). Dipping BP pattern was defined as nighttime/daytime SBP ratio < 0.9 while nondipping BP pattern was the ratio ≥0.9.

2.5. Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and compared by the independent student t-test, and categorical variables were presented as number and percentage of cases and compared by the chi-square test. Pearson correlation analysis was performed to evaluate the relationship between BMI with PAC and serum sodium level. Logistic regression analysis was used and pertinent variables were entered into the models in a tiered fashion, and the odds ratio of prevalent CVD was calculated for standardized increment of 1-SD of each BP component. All analyses were conducted in the SPSS 17.0 (Chicago, IL). All P values were 2 sided, and statistical significance was defined as P < 0.05.

3. Results

3.1. General characteristics

A total of 568 diabetic patients with hypertension were enrolled. As shown in Table 1, the mean age was 60.8 years, male participants accounted for 67.8% (n = 385) and 36.3% (n = 206) of participants were present cigarette smoking. The mean durations of diabetes and hypertension were 6.1 ± 3.4 years, respectively. The mean BMI was 25.4 ± 4.7 kg/m². A total of 117 participants (20.6%) had prevalent CVD, including 48 myoccardial infarction, 57 ischemic stroke, and 12 peripheral artery disease.

3.2. Comparisons between subjects with- and without CVD

All participants were divided into with- and without CVD groups and between-group differences were evaluated. As shown in Table 1, compared to subjects without CVD, those with CVD had statistically significant differences in terms of general characteristics. Particularly, the comparisons of age, male gender, body mass index, hypertension duration, diabetes duration, serum aldosterone concentration, eGFR, serum sodium, and serum potassium were observed. In addition, the use of antihypertensive medications and diabetes duration was also different between the two groups.

| Table 1 | General characteristics and comparisons by categories of with- and without CVD. |
|---------|---------------------------------------------------------------------|
| Variables | Overall (n = 568) | With CVD (n = 117) | Without CVD (n = 451) |
| Age, y | 60.8 ± 10.7 | 61.3 ± 9.9 | 60.1 ± 11.2 |
| Male, n (%) | 385 (67.8) | 78 (66.5) | 307 (88.1) |
| Present smoking, n (%) | 206 (36.3) | 44 (37.6) | 162 (55.9) |
| Body mass index, kg/m² | 25.4 ± 4.7 | 26.6 ± 4.3 | 25.0 ± 4.2 |
| Diabetes duration, y | 6.1 ± 2.7 | 6.3 ± 2.0 | 6.0 ± 2.3 |
| Hypertension duration, y | 4.6 ± 3.3 | 5.3 ± 2.9 | 5.6 ± 3.4 |
| Total cholesterol, mmol/L | 5.2 ± 0.7 | 5.2 ± 0.4 | 5.1 ± 0.9 |
| Triglyceride, mmol/L | 1.7 ± 0.3 | 2.1 ± 0.4 | 1.9 ± 0.5 |
| Fasting plasma glucose, mmol/L | 6.7 ± 1.2 | 6.8 ± 1.0 | 6.6 ± 1.1 |
| Glycated hemoglobin, % | 7.2 ± 1.2 | 7.3 ± 1.1 | 7.1 ± 1.2 |
| Creatinine, µmol/L | 126.5 ± 36.7 | 125.5 ± 33.6 | 125.8 ± 37.7 |
| PAC, ng/dL | 5.2 ± 1.7 | 5.6 ± 2.3 | 4.3 ± 1.8 |
| Sodium, mmol/L | 142.5 ± 4.6 | 145.3 ± 3.7 | 141.5 ± 3.0 |
| Potassium, mmol/L | 4.1 ± 0.4 | 4.0 ± 0.5 | 4.1 ± 0.3 |
| ALT, UL | 40.4 ± 46 | 42.9 ± 39 | 39.1 ± 30 |
| eGFR, ml/min/1.73 m² | 93.6 ± 14.9 | 92.8 ± 11.6 | 95.2 ± 14.4 |
| Anti-platelet, n (%) | 493 (86.8) | 117 (100) | 376 (85.4) |
| Statins, n (%) | 418 (73.6) | 117 (100) | 301 (66.7) |
| ACE/ARB, n (%) | 465 (81.9) | 95 (82.1) | 370 (82.0) |
| β-blocker, n (%) | 155 (27.6) | 33 (28.2) | 122 (27.1) |
| CCB, n (%) | 400 (70.4) | 82 (70.1) | 318 (70.5) |
| Diuretic, n (%) | 272 (47.9) | 54 (46.2) | 218 (48.3) |
| Oral hypoglycemic drugs, n (%) | 496 (87.7) | 102 (87.2) | 394 (87.8) |
| Insulin, n (%) | 133 (23.4) | 30 (25.6) | 103 (22.8) |

ACE/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker, ALT = alanine aminotransferase, CCB = calcium channel blocker, CVD = cardiovascular diseases, eGFR = estimated glomerular filtration rate, PAC = plasma aldosterone concentration.

*P < 0.05 versus without CVD group
significantly higher BMI (26.6 ± 4.3 kg/m² vs 25.0 ± 4.2 kg/m²), PAC (6.1 ± 2.3 ng/dL vs 4.3 ± 1.8 ng/dL), and serum sodium level (145.3 ± 3.7 mmol/L vs 141.5 ± 3.0 mmol/L). No significant differences in other variables such as antihypertensive medications and antidiabetic drugs usage were observed.

3.3. Comparisons of CBP and ABP by categories of with- and without CVD

As shown in Fig. 1, no significant between-group differences in clinic SBP and DBP were observed. However, with respect to ABP, 24 hour-SBP, daytime-SBP, and nighttime-SBP were all significantly higher in subjects with CVD than those without CVD (P < 0.05 for all comparisons). While no between-group differences in ambulatory DBP were observed. The nighttime/daytime SBP ratio was also significantly higher in subjects with CVD (0.95 ± 0.06 vs 0.91 ± 0.04, P < 0.05). The percentages of nondipping BP pattern in subjects with CVD versus without CVD were 73.5% (n=86) and 63.6% (n=287), respectively.

3.4. Pearson correlation analysis

Pearson correlation analysis showed that BMI were positively correlated with PAC and serum sodium level, with a correlation coefficient of 0.65 and 0.57 (P < 0.05), respectively (Fig. 2).

3.5. Logistic regression analyses

Logistic regression analyses were performed to evaluate the association of CBP and ABP with prevalent CVD, respectively. As shown in Table 2, both clinic-SBP and clinic-DBP were not significantly associated with prevalent CVD after adjusted for age, gender, cigarette smoking, TC, HbA1c, and BMI. In 24 hour-SBP, daytime-SBP, and nighttime-SBP, after additionally adjusted for PAC, no significant association with prevalent CVD was observed. In 24 hour-DBP, daytime-DBP, and nighttime-DBP, after additionally adjusted for clinic-DBP, no significant association with prevalent CVD was observed.

4. Discussion

Similar to prior studies,[13,14,18] our present study also shows that in diabetic hypertensive patients, ABP is superior to CBP in

![Figure 1](image1.png)

**Figure 1.** Comparison of BP components. *P < 0.05 versus without CVD group. BP = blood pressure, CVD = cardiovascular diseases.

![Figure 2](image2.png)

**Figure 2.** Relationship between BMI with PAC and serum sodium level. BMI = body mass index, PAC = plasma aldosterone concentration.

| BPs         | Model 1         | Model 2         | Model 3         | Model 4         | Model 5         |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| SBP category |                 |                 |                 |                 |                 |
| Clinic      | 2.04 (1.78–2.86) | 1.95 (1.47–2.58) | 1.26 (0.95–1.64) | NS              | NS              |
| 24 hours    | 2.27 (1.99–2.96) | 2.06 (1.62–2.78) | 1.84 (1.57–2.12) | 1.32 (1.20–1.93) | 1.19 (0.97–1.46) |
| Daytime     | 2.20 (1.86–2.83) | 2.00 (1.60–2.59) | 1.76 (1.46–2.03) | 1.29 (1.18–1.80) | 1.10 (0.95–1.29) |
| Nighttime   | 2.22 (1.96–2.96) | 2.02 (1.71–2.65) | 1.81 (1.50–2.08) | 1.30 (1.19–1.82) | 1.12 (0.96–1.30) |
| DBP category |                 |                 |                 |                 |                 |
| Clinic      | 1.97 (1.37–2.11) | 1.81 (1.20–1.93) | 1.14 (0.96–1.33) | NS              | NS              |
| 24h         | 1.99 (1.56–2.18) | 1.90 (1.36–2.00) | 1.38 (1.09–1.72) | 1.12 (0.99–1.34) | NS              |
| Daytime     | 1.90 (1.49–2.13) | 1.86 (1.42–2.02) | 1.27 (1.10–1.65) | 1.09 (0.95–1.28) | NS              |
| Nighttime   | 1.92 (1.53–2.10) | 1.84 (1.54–2.01) | 1.30 (1.11–1.70) | 1.11 (0.97–1.28) | NS              |

DBP = diastolic blood pressure, NS = nonsignificant, Model 1, unadjusted, Model 2, adjusted for age and male gender, Model 3, further adjusted for cigarette smoking, TC, HbA1c, and BMI, Model 4, further adjusted for either clinic SBP or clinic DBP in SBP or DBP category, Model 5, further adjusted for PAC, SBP, = systolic blood pressure.
In conclusion, our present study reveals that in diabetic hypertensive patients, ABP is superior to CBP in relation to prevalent CVD. Furthermore, aldosterone excess may be the potential mechanism contributing to the association between ABP and prevalent CVD. Future studies are needed to evaluate whether increased plasma aldosterone concentration could be used to predict CVD risk and whether aldosterone antagonist is beneficial for improving cardiovascular outcomes in these populations.

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References
[1] Kissela BM, Khoury J, Kleindorfer D, et al. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. Diabetes Care 2005;28:355–9.
[2] Adler AI, Stratton IM, Neaf HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412–9.
[3] Hypertension in Diabetes Study (HDS): Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. J Hypertens 1993;11:319–25.
[4] Sturrock ND, George E, Pound N, et al. Non-dipping circadian blood pressure and renal impairment are associated with increased mortality in diabetes mellitus. Diabet Med 2009;17:360–4.
[5] Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–72.
[6] Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2013;313:603–15.
[7] Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717.
[8] Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–85.
[9] Parati G, Stergiou G, O’Brien E, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 2014;32:1359–66.
[10] Cai A, Zhong Q, Liu C, et al. Association of systolic and diastolic blood pressure night-to-day ratios with atherosclerotic cardiovascular diseases. Hypertens Res 2016.
[11] Roush GC, Fagard RH, Salles GF, et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. J Hypertens 2014;32:2332–40. discussion 2340.
[12] Eguchi K, Pickering TG, Hoshide S, et al. Ambulatory blood pressure is a better marker than clinic blood pressure in predicting cardiovascular events in patients with without type 2 diabetes. Am J Hypertens 2008;21:443–50.
[13] Salles GF, Leite NC, Pereira BB, et al. Prognostic impact of clinic and ambulatory blood pressure components in high-risk type 2 diabetic patients: the Rio de Janeiro Type 2 Diabetes Cohort Study. J Hypertens 2013;31:2176–86.
[14] Nakano S, Ito T, Furuya K, et al. Ambulatory blood pressure level rather than dipper/nondipper status predicts vascular events in type 2 diabetic subjects. Hypertens Res 2004;27:647–56.
[15] Nakano S, Konishi K, Furuya K, et al. A prognostic role of mean 24-h pulse pressure level for cardiovascular events in type 2 diabetic subjects under 60 years of age. Diabetes Care 2005;28:95–100.
[16] Dudenbostel T, Ghazi I, Liu M, et al. Body mass index predicts 24-hour urinary aldosterone levels in patients with resistant hypertension. Hypertension 2016;68:995–1003.
[17] Papaefth GS, Papakyrakou P, Panagiotou TN. Central obesity, type 2 diabetes and insulin: exploring a pathway full of thorns. Arch Med Sci 2015;11:463–82.
[18] Laugesen E, Rossen NB, Poulsen PL, et al. Pulse pressure and systolic night-day ratio interact in prediction of macrovascular disease in patients with type 2 diabetes mellitus. J Hum Hypertens 2012;26:164–70.
[19] Wright JT, Whelton PK, Reboussin DM. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2016;374:2294.
[20] Schwartz JE, Burg MM, Shimbo D, et al. Clinic blood pressure underestimates ambulatory blood pressure in an untreated employer-based US population: results from the masked hypertension study. Circulation 2016;134:1794–807.
[21] Zbroch E, Musialowska D, Koc-Zorawska E, et al. Age influence on renalase and catecholamines concentration in hypertensive patients, including maintained dialysis. Clin Interv Aging 2016;11:1545–50.
[22] Muñoz-Durango N, Fuentes CA, Castillo AE, et al. Role of the renin-angiotensin-aldosterone system beyond blood pressure regulation: molecular and cellular mechanisms involved in end-organ damage during arterial hypertension. Int J Mol Sci 2016;17: