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Spironolactone is superior to hydrochlorothiazide for blood pressure control and arterial stiffness improvement

A prospective study

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Abstract

The present study is to investigate whether spironolactone is better than hydrochlorothiazide (HCTZ) for blood pressure (BP) control and arterial stiffness improvement. Five-hundred-sixty-six uncontrolled hypertensive patients with 2 different classes of antihypertensive medications treatment were enrolled. Spironolactone or HCTZ was randomly prescribed for 4 weeks. Carotid-femoral pulse wave velocity (cf-PWV) was measured at baseline and after 4 weeks' of spironolactone or HCTZ treatment. Between-group differences were evaluated, and logistic regression analysis was performed to evaluate the association of cf-PWV increase and incident resistant hypertension. No significant differences in baseline characteristics were observed between spironolactone and HCTZ groups. After 4 weeks' treatment, both systolic BP and cf-PWV were reduced more profoundly in spironolactone group versus HCTZ group ($P < .05$). Pearson and Spearman correlation analysis showed that age, diabetes mellitus, and HCTZ were positively correlated with cf-PWV, while spironolactone was negatively with cf-PWV. Logistic regression analysis indicated that per 1-standard deviation increase in cf-PWV was associated with 92% higher incidence of resistant hypertension. After adjusted for spironolactone, no significant association between cf-PWV increase and incident resistant hypertension was observed, indicating that the adverse effect of arterial stiffness on resistant hypertension development might be reversed by spironolactone treatment. In summary, uncontrolled hypertensive patients with spironolactone treatment appear to have better BP control and arterial stiffness improvement.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CCB = calcium channel blocker, cf-PWV = carotid-femoral pulse wave velocity, CRP = C-reactive protein, FPG = fasting plasma glucose, HCTZ = hydrochlorothiazide, SBP/DBP = systolic/diastolic blood pressure.

Keywords: arterial stiffness, hypertension, spironolactone

1. Introduction

Numerous epidemiological studies have shown that the prevalence of resistant hypertension, which is defined as clinic systolic and/or diastolic blood pressure (SBP/DBP) ≥ 140/90 in spite of using ≥ 3 different classes of antihypertensive medications, is gradually increasing.[1–4] Notably, sustained BP elevation contributes to target organs damage, cardiovascular and renal events and premature death.[5–7] Therefore, BP control is essential for preventing resistant hypertension development and reducing cardiovascular events.[8]

According to the 2008 American Heart Association Scientific Statement,[1] thiazide diuretic such as hydrochlorothiazide (HCTZ) is recommended as the first line medication for resistant hypertension management. Spironolactone, a potassium-sparing diuretic, is recommended as the fourth line medication if BP could not control despite using optimal doses of 3 different classes of antihypertensive medications.[1]

In recent 2 decades, accumulating evidence has revealed that arterial stiffness is an independent risk factor of hypertension, coronary heart disease and cerebrovascular disease. Blood pressure elevation leads to arterial stiffness, which in turn makes BP difficult to control.[9–11] Therefore, it is reasonable to anticipate that improved arterial stiffness would be beneficial for BP control and resistant hypertension prevention. Prior experimental studies showed that aldosterone antagonist has potent effects on improving vascular fibrosis via inhibiting fibroblast proliferation and improving endothelial function. Clinical studies also suggested that arterial stiffness could be improved by salt restriction and aldosterone antagonist therapy in hypertensive patients.[12,13]

We therefore conducted a prospective study to evaluate the differences in BP control and arterial stiffness improvement between HCTZ versus spironolactone treatment in patients with uncontrolled hypertension.

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The authors have no conflicts of interest to disclose.

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2. Methods

2.1. Study participants

Study participants were enrolled after informed consent was obtained and current study was approved by the Research Ethic Committee of The Third People's Hospital of Huizhou. Included criteria were as follows: hypertensive patients with clinic SBP and/or DBP ≥ 140/90 mm Hg and were treating with optimal doses of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and calcium channel blocker (CCB), and without contraindications to HCTZ or spironolactone treatment. Excluded criteria were as follows: documented secondary hypertension, pregnant women, have myocardial infarction, ischemic stroke, atrial fibrillation or congestive heart failure in the past 6 months. All the performances were in accordance to the Declaration of Helsinki.

2.2. Medications prescription

Participants were prescribed HCTZ (25 mg/qd) if the last digit of their telephone numbers was odd, or prescribed spironolactone (25 mg/qd) if the last digit of their telephone numbers was even. In specific, HCTZ was prescribed as a single pill rather than a combined medication. The duration of treatment was 4 weeks and other antihypertensive medications were without changes. During the periods of active treatment, participants were follow-up by investigator every 2 weeks by telephone and no side effects were reported.

2.3. Data collection

Demographic data including age, gender, smoking status, previous medical history, and current medications usage were collected using self-administered questionnaire; anthropometric data including body weight, height, SBP/DBP, and heart rate at rest were measured by investigators in accordance to guideline recommendation.[14] In brief, BP was measured 3 times and the last 2 BP readings were averaged to obtain the clinic BP. Body mass index (BMI) was calculated by body weight in kilogram divided by height in squared meter. Overnight fasting venous blood was drawn for electrolytes, creatinine, fasting plasma glucose (FPG), lipid profiles, uric acid, and C-reactive protein (CRP) measurements.

2.4. Arterial stiffness measurement

At baseline and after 4 weeks of HCTZ or spironolactone treatment, carotid-femoral pulse wave velocity (cf-PWV) was assessed to determine arterial stiffness, and all the procedures were performed in accordance to guideline recommendation[15] by 2 independent investigators who were blinded to the treatment allocation (Atcor Medical Blood Pressure Analysis System, Sydney Australia). Measurement was done at the right common carotid and common femoral arteries and the distance between these 2 points were calculated by a tape, and the travel time of pulse wave between these 2 points were measured and calculated by the device automatically.

2.5. Statistical analysis

Continuous variables were presented as mean ± SD and categorical variables were presented as number and percentages of cases. Student *t* test for continuous variables comparison and the chi-square or Fisher exact test for categorical variables comparison were conducted. Pearson or Spearman correlation analysis was used to evaluate the relationship between cf-PWV and age, male gender, BMI, SBP, uric acid, CRP, diabetes mellitus, statins, spironolactone, and HCTZ after 4 weeks' treatment. Logistic regression analysis was used to evaluation the association between per 1-SD standardized increase cf-PWV and incidence of resistant hypertension. Covariates were entered in a stepwise model. Potential interaction between cf-PWV and HTCZ and spironolactone was evaluated and no significant interaction was observed. Statistical analyze were computed using SPSS 17.0 (SPSS Inc, Chicago, IL). All statistical tests were two-sided and considered statistically significant when $P < .05$.

3. Results

3.1. Baseline characteristics

From January of 2015 to June of 2017, we had totally screened 609 uncontrolled hypertensive patients in our outpatient clinic. Among them, 3 had secondary hypertension, 2 pregnant women, 11 had myocardial infarction, 8 ischemic stroke, 11 atrial fibrillation, and 8 congestive heart failure in the past 6 months. Finally, a total of 566 patients were included into final analysis. The mean age was 55.6 ± 13.7 years, and male participants accounted for nearly 58%. Nearly 33%, 28%, and 17% of participants had cigarette smoking, type 2 diabetes mellitus, and angiographically diagnosed coronary heart disease, respectively. The mean SBP and DBP were 143 ± 13 mm Hg and 94 ± 10 mm Hg, respectively. The mean cf-PWV was 9.9 ± 1.2 m/s, with arterial stiffness prevalence was 32% in accordance to the cutoff value of 10 m/s as indicated by guideline.[15] Other baseline characteristics were presented in Table 1.

Table 1

Baseline characteristics comparisons between HCTZ and spironolactone groups.

Variables	Overall	HCTZ	Spironolactone
N	566	294 (52)	272 (48)
Age, years	55.6 ± 13.7	54.8±11.9	56.4±13.9
Male n (%)	328 (58)	168 (57)	160 (59)
SBP, mm Hg	143 ± 13	142±14	143±11
DBP, mm Hg	94 ± 10	93±9	94±11
HR, bpm	74 ± 20	75±22	72±17
Body weight, kg	66 ± 23	64±21	67±23
Height, m	1.67 ± 0.15	1.66±0.18	1.69±0.14
BMI, kg/m^2	23.6 ± 2.5	23.0±2.1	23.9±2.6
Cigarette smoker n (%)	187 (33)	100 (34)	87 (32)
T2DM n (%)	158 (28)	82 (28)	76 (28)
CHD n (%)	96 (17)	47 (16)	49 (18)
Creatinine, μmol/L	81.6 ± 15.7	79.3±14.2	82.7±15.9
FPG, mmol/L	6.0 ± 1.2	6.2±1.0	5.8±1.2
TG, mmol/L	1.8 ± 1.1	1.8±1.2	1.7±1.0
TC, mmol/L	5.0 ± 1.2	5.1±1.1	5.0±1.2
LDL-C, mmol/L	3.2 ± 1.0	3.2±1.2	3.0±1.0
HDL-C, mmol/L	1.1 ± 0.4	1.0±0.3	1.1±0.4
Uric acid, μmol/L	398 ± 45	403±50	392±41
CRP, mg/L	8.2 ± 4.3	8.5±4.7	7.9±4.0
Sodium, mmol/L	142 ± 5	144±6	141±5
Potassium, mmol/L	4.1 ± 0.3	4.1±0.4	4.0±0.3
cf-PWV, m/s	9.9 ± 1.2	9.8±1.4	10.0±1.1
Arterial stiffness n (%)	180 (32)	91 (31)	89 (33)

BMI = body mass index, bpm = beat per minute, cf-PWV = carotid femoral-pulse wave velocity, CHD = coronary heart disease, CRP = C-reactive protein, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL-C = high density lipoprotein cholesterol, HR = heart rate, LDL-C = low density lipoprotein cholesterol, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglyceride.

Table 2

Comparisons of medications between HCTZ and spironolactone groups.

Variables	Overall	HCTZ	Spironolactone
N	566	294	272
CCB n (%)	566 (100)	294 (100)	272 (100)
ACEI n (%)	230 (41)	118 (40)	112 (41)
ARB n (%)	336 (59)	176 (60)	160 (59)
Aspirin n (%)	137 (24)	68 (23)	69 (25)
Statins n (%)	128 (23)	74 (25)*	54 (20)
Antidiabetic medications n (%)	120 (21)	68 (23)	52 (19)
Insulin n (%)	48 (8)	26 (9)	22 (8)
Allopurinol n (%)	16 (3)	9 (3)	7 (3)

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker.
* $P < .05$ versus spironolactone group.

3.2. Baseline characteristics comparisons between HCTZ and spironolactone groups

A slightly higher proportion of participants were prescribed HCTZ versus spironolactone (52% versus 48%). As presented in Table 1, no significant differences in baseline characteristics were observed between HCTZ and spironolactone groups.

3.3. Baseline medications comparisons between HCTZ and spironolactone groups

Baseline medications usages were compared between HCTZ and spironolactone groups. As shown in Table 2, no significant differences in medications usage were observed, except for higher percentage of statins usage in HCTZ group versus spironolactone group.

3.4. Comparisons of BP and cf-PWV after 4 weeks' treatment

As presented in Table 3, after 4 weeks' treatment, SBP was reduced more profoundly in spironolactone group versus HCTZ group (130 ± 10 mm Hg vs 134 ± 9 mm, $P < .05$). In addition, cf-PWV was also reduced more profoundly in spironolactone group versus HCTZ group (9.6 ± 1.3 mm Hg vs 9.9 ± 1.4 mm, $P < .05$). Although the percentage of participants developing resistant hypertension was lower in spironolactone group versus HCTZ group (41% vs 45%), but the difference did not achieve statistical significance ($P = .063$).

3.5. Pearson and Spearman correlation analysis

After 4 weeks' treatment, Pearson and Spearman correlation analysis was performed to evaluate the relationship between cf-PWV and parameters of interest. As presented in Table 4, age, type 2 diabetes mellitus, and HCTZ were all positively correlated with cf-PWV, while spironolactone was negatively correlated with cf-PWV.

Table 3

Comparisons of BP and cf-PWV after 4 weeks treatment.

Variables	HCTZ (n = 294)	Spironolactone (n = 272)
SBP, mm Hg	134±9	130±10*
DBP, mm Hg	84±7	82±8
HR, bpm	72±16	71±13
cf-PWV, m/s	9.9±1.4	9.6±1.3*
Resistant hypertension n (%)	133 (45)	112 (41)

bpm = beat per minute, cf-PWV = carotid femoral-pulse wave velocity, DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure.
* $P < .05$.

Table 4

Correlation between cf-PWV and parameters of interest.

Variables	Correlation coefficient	*P* value
Age, years	0.45	<.001
Male	0.08	.651
BMI, kg/m^2	0.06	.893
T2DM	0.26	.013
CRP, mg/L	0.20	.099
Uric acid, μmol/L	0.15	.128
HCTZ	0.21	.036
Spironolactone	−0.28	.008
Statins	−0.17	.075

BMI = body mass index, CRP = C-reactive protein, T2DM = type 2 diabetes mellitus.

3.6. Logistic regression analysis

As showed in Table 5, in unadjusted model, increased cf-PWV was significantly associated with a 92% higher incidence of resistant hypertension. With stepwise adjustment for potential confounding factors, the hazard ratio was gradually reduced. In model 4, after additionally adjusted for HCTZ, no significant change of hazard ratio was observed; nevertheless, in model 5, after additionally adjusted for spironolactone, the hazard ratio was substantially reduced and no significant association between cf-PWV and incident resistant hypertension was observed, indicating that the adverse effect of arterial stiffness on resistant hypertension development might be reversed by spironolactone treatment.

4. Discussion

The present study has the following principal findings. First, in uncontrolled hypertensive patients with optimal doses of ACEI/ARB and CCB treatment, adding spironolactone is better than adding HCTZ for SBP and cf-PWV reduction. Second, correlation analysis suggests that HCTZ is positively correlated with cf-PWV while spironolactone is negatively correlated with cf-PWV. Third, the detrimental effect of arterial stiffness on resistant hypertension development may be reversed by spironolactone treatment. Future randomized double-blinded controlled trials are warranted to evaluate whether long-term spironolactone treatment could improve arterial stiffness, decrease incident resistant hypertension, and improve cardiovascular prognosis.

Table 5

Logistic regression analyses of cf-PWV and incidence of resistant hypertension.

	Hazard ratio	95% Confidence interval
Unadjusted	1.92	1.67–2.43
Model 1	1.59	1.30–2.06
Model 2	1.41	1.28–1.85
Model 3	1.20	1.08–1.37
Model 4	1.17	1.06–1.34
Model 5	1.05	0.94–1.18

Model 1 adjusted for age and male gender; Model 2 further adjusted for cigarette smoking and type 2 diabetes mellitus; model 3 further adjusted for C-reactive protein and uric acid; Model 4 further adjusted for HCTZ; Model 5 further adjusted for spironolactone.

Numerous cross-sectional studies reveal that patients with resistant hypertension have higher prevalence of co-morbidities such as coronary heart disease, ischemic stroke, congestive heart failure, and chronic kidney disease.[16] In addition, prospective cohort studies also indicate that resistant hypertension is an independent risk factor of cardiovascular and renal events.[3,17,18] Therefore, it is clinically relevant to prevent resistant hypertension development. Arterial stiffness, featured by vascular fibrosis and endothelial dysfunction, is a major risk factor of hypertension.[9,10] Moreover, hypertension per se could lead to arterial stiffening, which in turn causes BP elevation.[11] Therefore, one may anticipate that improved arterial stiffness would be beneficial for BP control. Indeed, prior studies showed that spironolactone could reduce BP via improving arterial stiffness.[22]

Thiazide diuretic is the first line medication for resistant hypertension treatment.[1] Nevertheless, some studies have revealed that thiazide diuretic has unwanted effects such as impairing glucose metabolism, inducing insulin resistance, and enhancing sympathetic nerve activity.[19,20] These pathological alterations could result in arterial stiffness. In contrast, besides lowering BP, aldosterone antagonist has documented pleiotropic effects including improving endothelial function, anti-inflammation and antifibrosis.[21–23] Therefore, one may anticipate that spironolactone treatment would be better than HCTZ for arterial stiffness improvement and BP control. Results from the present study support this hypothesis. As presented in Table 3, after 4 weeks' spironolactone treatment, SBP and cf-PWV were reduced more profoundly than HCTZ. In addition, correlation analysis indicates that HCTZ usage correlates with arterial stiffness while spironolactone treatment may improve arterial stiffness. In addition, results from logistic regression analysis further strengthen these findings. As shown in logistic regression model, after adjusted for spironolactone, the independent association of arterial stiffness and incident resistant hypertension was attenuated to nonsignificant. A prior prospective cross-over study also indicated that in elderly uncontrolled hypertensive patients with concurrently amlodipine and candesartan treatment.[24] spironolactone treatment seemed to be better than chlorthalidone as add-on treatment due to its effect on endothelial protection and inflammation amelioration. However, one should be cautious that the combination of ACEI or ARB and spironolactone increases the risk of hyperkalemia and patients should be closely monitored serum potassium level.

The strength of current study is the prospective design and a large sample size. The limitations of current study include the followings: first, it was not a truly randomized and double-blinded design, and the duration of follow-up was only 4 weeks. Second, thiazide diuretic such as chlorthalidone has more potent efficacy than HCTZ, and whether chlorthalidone therapy would have differing effects on BP control and arterial stiffness improvement compared to HCTZ is unknown. Since in mainland of China is lacking chlorthalidone, future study in investigating this hypothesis is warranted in areas where chlorthalidone is available. Third, peripheral arterial disease may alter blood pressure and cf-PWV values. However, our current study did not evaluate the potential peripheral arterial disease and therefore we could not adjust for the potential covariates in the regression model. To our knowledge, concurrent peripheral arterial disease indeed would influence cf-PWV change and blood pressure measurement. In future study, it is warranted to evaluate peripheral arterial disease and to investigate whether and to what extent peripheral arterial disease will influence cf-PWV and blood pressure change

5. Conclusion

In summary, our present study indicates that in uncontrolled hypertensive patients, adding spironolactone appears to be better than HCTZ for SBP control, cf-PWV reduction and prevention of resistant hypertension development.

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