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Efficacy of Spironolactone Therapy in Patients With True Resistant Hypertension

Inter-American Society of Hypertension

Fabio de Souza, Elizabeth Muxfeldt, Roberto Fiszman, Gil Salles

Abstract—The role of spironolactone in resistant hypertension management is unclear. The aim of this prospective trial was to evaluate the antihypertensive effect of spironolactone in patients with true resistant hypertension diagnosed by ambulatory blood pressure monitoring. A total of 175 patients had clinical and complementary exams obtained at baseline and received spironolactone in doses of 25 to 100 mg/d. A second ambulatory blood pressure monitoring was performed after a median interval of 7 months. Paired Student *t* test was used to assess differences in blood pressure before and during spironolactone administration, and multivariate analysis adjusted for age, sex, and number of antihypertensive drugs to assess the predictors of blood pressure fall. There were mean reductions of 16 and 9 mm Hg, respectively, in 24-hour systolic and diastolic blood pressures (95% CIs: 13 to 18 and 7 to 10 mm Hg; $P<0.001$). Office systolic blood pressure and diastolic blood pressure also decreased (14 and 7 mm Hg). Controlled ambulatory blood pressure was reached in 48% of patients. Factors associated with better response were higher waist circumference, lower aortic pulse wave velocity, and lower serum potassium. No association with plasma aldosterone or aldosterone:renin ratio was found. Adverse effects were observed in 13 patients (7.4%). A third ambulatory blood pressure monitoring performed in 78 patients after a median of 15 months confirmed the persistence of the spironolactone effect. In conclusion, spironolactone administration to true resistant hypertensive patients is safe and effective in decreasing blood pressure, especially in those with abdominal obesity and lower arterial stiffness. Its addition to an antihypertensive regimen as the fourth or fifth drug is recommended. (*Hypertension*. 2010;55:00-00.)

Key Words: ambulatory blood pressure monitoring ■ resistant hypertension ■ spironolactone

Resistant hypertension (RH) is a common clinical condition defined as the failure to control office blood pressure (BP) despite a treatment with ≥ 3 different classes of antihypertensive drugs in optimal dosages, ideally including a diuretic.¹ Previous surveys have shown prevalence ranges from 10% to $\approx 30\%$.¹ Although there is no consensus about the better therapeutic scheme for resistant hypertensive patients, in general, diuretics, angiotensin-blocking agents, calcium-channel blockers, and β -blockers are used as the first-line choices. However, there is a lack of evidence about the optimal choice of a fourth- or fifth-line antihypertensive drug, and in this context there has been increasing interest in the role of aldosterone antagonists, particularly spironolactone.

The efficacy and safety of spironolactone in reducing BP were demonstrated >2 decades ago.² Over the past 15 years, after many reports had suggested that primary hyperaldosteronism is probably more common than it was regarded previously,^{3,4} several studies have been dedicated to evaluate the spironolactone effect in patients with refractoriness to treatment, most demonstrating that low-dose spironolactone actually provides BP reduction in resistant hypertensive

subjects with or without underlying hyperaldosteronism.^{5–10} However, many of these studies evaluated a small number of patients,^{6,8–10} some included patients who did not fulfill criteria for RH,^{5–7,10} and in most of them only office BP was assessed.^{5–9} By doing so, the white-coat effect, which underlies resistant to treatment in $\leq 40\%$ of adherent resistant hypertensive patients,¹¹ was neglected.

Therefore, the objective of this prospective open trial was to evaluate the antihypertensive effect of spironolactone in patients with true RH confirmed and followed-up by ambulatory BP monitoring (ABPM). We also aimed to investigate factors that could be related to better antihypertensive response, including measurements of aldosterone excess.

Methods

Patients and Baseline and Follow-Up Procedures

We conducted an open-label prospective trial on the use of spironolactone in the management of patients with true RH. Between April 2007 and September 2008, 236 resistant hypertensive patients were consecutively evaluated in the hypertension outpatient clinic of our university hospital. All of the participants gave written informed

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consent, and the local research ethics committee had previously approved the study protocol. The enrollment criteria, baseline protocol, and diagnostic definitions have been detailed previously.^{11,12} In brief, all of the hypertensive patients referred who fulfilled the criteria for RH (office BP $\geq 140/90$ mm Hg; using ≥ 3 antihypertensive drugs in optimal dosages, including a diuretic; and considered at least moderately adherent using a standard validated questionnaire¹³) were submitted to a standard protocol that included complete clinical examination, laboratory evaluation, 2D echocardiography, 24-hour ABPM, and carotid-femoral pulse wave velocity (PWV) measurement.

Office BP was measured twice, in the sitting position, using a digital BP monitor Omron HEM-907 XL with a suitably sized cuff, and the BP considered was the mean between the 2 readings. Echocardiographic left ventricular mass was calculated by the Devereux formula¹⁴ and indexed to body surface area (left ventricular mass index). Left ventricular hypertrophy was defined as left ventricular mass index >125 g/m² in men and >110 g/m² in women. The ABPM was recorded using Mobil-O-Graph (version 12, Dynamap, Cardios) equipment, approved by the British Society of Hypertension.¹⁵ Readings were taken every 15 minutes throughout the day and every 30 minutes at night. Variables evaluated were mean 24-hour, daytime, and nighttime systolic BP (SBP) and diastolic BP (DBP). The nighttime period was ascertained for each individual patient from registered diaries. After ABPM, patients were classified as true RH if mean 24-hour BP was $\geq 130/80$ mm Hg. Carotid-femoral (aortic) PWV was measured in the morning just after the ABPM examination with the Complior equipment (Artech-Medical), validated previously.¹⁶ Three consecutive measurements were performed, and the mean value was used.

Laboratory evaluation included serum lipids, glucose, electrolytes, and creatinine after an overnight fasting. A baseline serum creatinine level >132 μ mol/L or potassium level >5.5 mmol/L was the exclusion criteria. Plasma aldosterone concentration (PAC), plasma renin activity, and aldosterone:renin ratio (ARR) were obtained according to protocol reported previously.¹⁷ For calculation of ARR, plasma renin activity was corrected to 0.5 ng/mL per hour when less than this value; consequently, no patients with PAC <15 ng/dL were considered to have an ARR ≥ 30 .¹⁸ Patients with ARR ≥ 30 , unilateral adrenal alterations in abdominal computed tomography scan, and nonsuppressible PAC after a saline infusion test were identified as having surgical curable subtype of primary aldosteronism (aldosterone-producing adenoma) and were not included in this study.

Figure 1 outlines the flowchart of the study. Spironolactone was initiated at a dose of 25 mg/d to patients with true RH on first ABPM. Follow-up visits were at 2, 4, and 6 months and included assessment of tolerance to treatment, office BP measurements, and serum creatinine and potassium evaluation. Depending on these factors, the dosage could be titrated up to 50 and 100 mg during this period, and then a second ABPM was performed (after a median of 7 months). If controlled office BP was reached, ABPM could be repeated earlier than 6 months. A third ABPM was performed in a subsample of patients to evaluate the persistence of spironolactone effect after 6 to 12 months. All of the other antihypertensive treatment was kept unchanged throughout the study.

Statistical Analysis

Statistical analyses were performed using SPSS version 13.0 (SPSS Inc). Continuous variables are described as means (SDs) if normally distributed and as medians (interquartile range) if asymmetrically distributed. Paired Student *t* test was used to assess differences in office and ambulatory BPs before and after spironolactone administration on an intention-to-treat basis. Ambulatory BP response to spironolactone was also evaluated as the percentage change from baseline values [(first BP–second BP/first BP) $\times 100$] and considered satisfactory if $>10\%$, separately for SBP and DBP. Unpaired *t* test, Mann–Whitney test, and χ^2 test were used, when adequate, to compare patients with satisfactory and unsatisfactory BP responses.

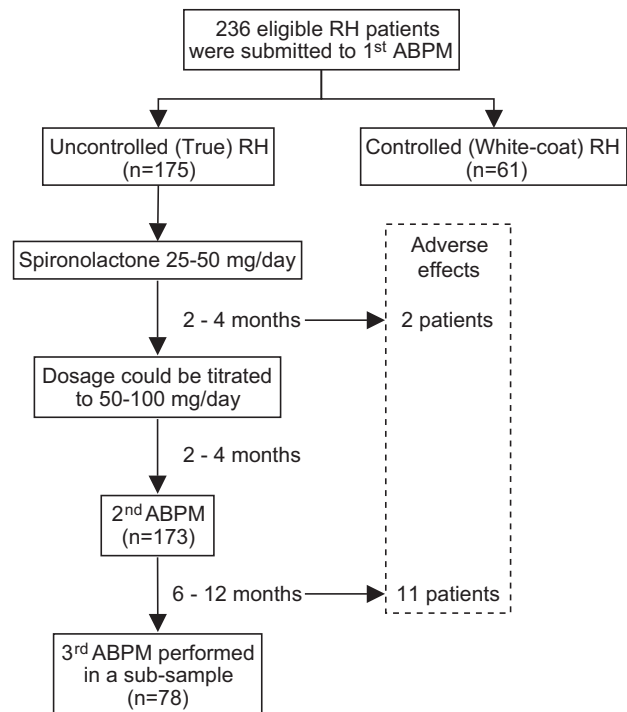


Figure 1. The flowchart of the study.

Finally, to assess the predictors of a satisfactory BP response, both a multiple linear regression (with a continuous percentage BP reduction as the dependent variable) and a multivariate logistic regression (with percentage BP reduction $>10\%$ as the dependent variable) were performed. Both analyses were further adjusted for age, sex, and number of antihypertensive drugs in use at baseline. A *P* value <0.05 was considered to be statistically significant.

Results

A total of 175 subjects (75%) had a diagnosis of true RH and received spironolactone according to the protocol. Table 1 outlines the baseline characteristics of these patients (72% women; mean [SD] age: 62.0 [10.0] years). Second ABPM was performed in 173 patients between 3 and 9 months (median: 7 months) after the first one (Figure 1). The median spironolactone dose was 50 mg (range: 25 to 100 mg). The median number of antihypertensive drugs was 4 (range: 3 to 6) before spironolactone, meaning that spironolactone was the median fifth drug added to antihypertensive therapy.

Figure 2 shows office and ambulatory SBPs and DBPs before and during spironolactone use. The mean decrease in 24-hour SBP and DBP was 16 mm Hg (95% CI: 13 to 18 mm Hg) and 9 mm Hg (95% CI: 7 to 10 mm Hg), respectively. These figures correspond with mean relative reductions of 10.2% for SBP and 9.5% for DBP. Office BPs also decreased a mean of 14 mm Hg (95% CI: 9 to 18 mm Hg) in SBP and 7 mm Hg (95% CI: 4 to 9 mm Hg) in DBP. Analyses of daytime and nighttime BPs showed comparable BP reductions, and all of the comparisons were significant ($P<0.001$). Controlled ambulatory BP (daytime BP $<135/85$ mm Hg) was reached in 48% of patients. Patients using 100 mg/d of spironolactone (31 patients) did not have greater BP reduction in office or ABPM than those using 25 to 50 mg/d.

Table 1. Baseline Characteristics of All of the Patients With True Resistant Hypertension Studied (n=175)

Characteristics	Values*
Sex, % female	72.4
Age, y	62 (10)
Waist circumference, cm	100 (11)
BMI, kg/m	30.2 (5.1)
Diabetes mellitus, %	33.1
Current smoking, %	9.9
Physical inactivity, %	69.2
Dyslipidemia, %	85.5
Previous cardiovascular diseases, %	51.7
Antihypertensive drugs, No.	4 (3 to 5)
Diuretics, %	100
ACE inhibitors/AR blockers, %	94
β -Blockers, %	85
Calcium channel blockers, %	71
Direct vasodilators, %	46
Central α -agonists, %	23
SBP, mm Hg	
Office	169 (27)
24 h	149 (14)
Daytime	151 (15)
Nighttime	139 (18)
DBP, mm Hg	
Office	92 (18)
24 h	86 (11)
Daytime	88 (12)
Nighttime	79 (12)
Echocardiographic LVH, %	75.6
Aortic PWV, m/s	10.4 (2.0)
Laboratory variables	
Serum potassium, mEq/L	4.2 (0.5)
Serum creatinine, μ mol/L	70 (61 to 88)
Plasma aldosterone, ng/dL	11.7 (7.8 to 16.4)
PRA, ng/mL per h	0.9 (0.3 to 3.3)
Plasma aldosterone/PRA (or ARR) [†]	10.3 (3.0 to 26.0)
Glucose, mmol/L	6.8 (2.9)
Total cholesterol, mmol/L	5.3 (1.1)
HDL cholesterol, mmol/L	1.2 (0.3)
Microalbuminuria (mg/24 h)	9.8 (5.8 to 19.1)

BMI indicates body mass index; ACE, angiotensin-converting enzyme; AR, angiotensin II receptor; LVH, left ventricular hypertrophy; PRA, plasma renin activity; HDL, high-density lipoprotein.

*Values are mean (SD) or proportions, except for number of antihypertensive drugs, serum creatinine, aldosterone, PRA, aldosterone:renin ratio, and microalbuminuria that are median (interquartile range).

[†]Values of PRA <0.5 ng/mL per hour were considered equal to 0.5 ng/mL per hour to calculate ARR.

Patients with a satisfactory SBP response had higher waist circumference and lower aortic PWV than those with unsatisfactory responses and also had a trend toward a greater body mass index and lower serum potassium. No difference in

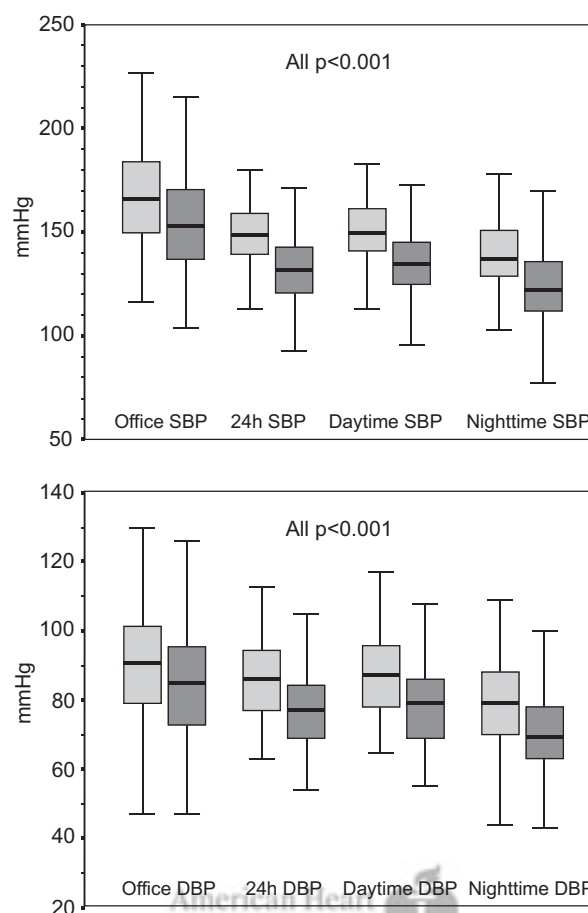


Figure 2. Box-plot graphic representation of office and ambulatory systolic (top) and diastolic (bottom) blood pressure before (clear box) and during (dark box) spironolactone administration. *P* values refer to paired *t* test comparisons of BPs before and during spironolactone use.

PAC, plasma renin activity, and ARR was observed between the 2 groups (Table 2).

In a multiple linear regression, a higher waist circumference, a lower aortic stiffness, and a lower serum potassium level were the covariates independently associated with a greater SBP reduction during spironolactone use (Table 3). Table 4 shows the independent predictors of a satisfactory SBP decline. Again, a higher waist circumference and a lower aortic PWV were the predictors of a satisfactory antihypertensive effect of spironolactone. The same analysis performed for the DBP response provided no significant associations. To further adjust the multivariate analyses for the specific classes of antihypertensive medication in use did not significantly change any of the results at all (data not shown).

A third ABPM was performed in 78 patients a median of 8 months after the second one. The median dose of spironolactone, as well as the median number of antihypertensive drugs in use, in this third ABPM was equal to that in the second ABPM. There were no differences in ambulatory BPs between the 2 exams, confirming the persistence of the antihypertensive effect over a median of 15 months (interquartile range: 13 to 20 months).

Table 2. Bivariate Comparisons of Baseline Characteristics Between Patients With Satisfactory (>10%) and Unsatisfactory BP Responses (≤10%) to Spironolactone

Characteristics	SBP Response			DBP Response		
	≤10%	>10%	P	≤10%	>10%	P
Sex, % female	71.6	72.8	0.86	76.7	67.5	0.23
Age, y	62 (11)	61 (9)	0.30	62 (10)	61 (10)	0.30
Waist circumference, cm	98 (12)	102 (10)	0.04	99 (11)	102 (11)	0.05
BMI, kg/m	29.5 (5.0)	30.9 (5.1)	0.08	30.0 (4.9)	30.6 (5.3)	0.37
Diabetes mellitus, %	28.4	36.3	0.33	33.3	31.7	0.87
Current smoking, %	11.1	8.8	0.62	11.1	8.5	0.62
Physical inactivity, %	66.7	71.4	0.51	67.8	70.7	0.74
Dyslipidemia, %	86.3	84.9	0.83	85.1	86.1	1.00
Previous cardiovascular diseases, %	51.9	51.1	0.99	52.2	50.6	0.88
Antihypertensive drugs, n	4 (3 to 5)	4 (3 to 5)	0.39	4 (3 to 5)	4 (3 to 5)	0.48
Echocardiographic LVH, %	75.3	75.9	0.99	76.3	75.0	0.99
Aortic PWV, m/s	10.8 (2.1)	10.0 (1.9)	0.03	10.6 (2.1)	10.2 (2.0)	0.12
Serum potassium, mEq/L	4.3 (0.5)	4.1 (0.5)	0.09	4.2 (0.5)	4.1 (0.4)	0.24
Serum creatinine, μmol/L	71 (62 to 88)	71 (62 to 88)	0.27	71 (62 to 88)	71 (62 to 88)	0.93
Plasma aldosterone, ng/dL	12.0 (8.0 to 16.0)	11.6 (7.1 to 18.0)	0.63	11.0 (7.5 to 15.6)	12.6 (9.1 to 18.3)	0.13
PRA, ng/mL per h	1.0 (0.3 to 3.0)	0.7 (0.3 to 3.7)	0.82	1.3 (0.3 to 2.9)	0.7 (0.4 to 2.8)	0.54
ARR	10.4 (4.4 to 23.0)	10.2 (2.3 to 27.0)	0.46	10.0 (3.8 to 21.3)	13.1 (2.7 to 32.1)	0.12
Glucose, mmol/L	6.7 (3.2)	6.8 (2.6)	0.86	6.9 (3.1)	6.7 (2.6)	0.66
Total cholesterol, mmol/L	5.3 (1.1)	5.3 (1.2)	0.98	5.3 (1.0)	5.4 (1.2)	0.45
HDL cholesterol, mmol/L	1.1 (0.3)	1.2 (0.4)	0.39	1.2 (0.3)	1.2 (0.4)	0.30
Microalbuminuria, mg/24 h	10.5 (5.6 to 18.5)	8.6 (5.9 to 20.0)	0.94	10.3 (5.8 to 18.0)	9.6 (5.7 to 26.9)	0.70

Values are as in Table 1: means (SD) or medians (interquartile range) and proportions. BMI indicates body mass index; LVH, left ventricular hypertrophy; PRA, plasma renin activity; HDL, high-density lipoprotein.

Adverse Effects

During follow-up, 13 patients (7.4%) had adverse effects attributed to spironolactone. Gynecomastia or breast discomfort occurred in 7 subjects (4%), resulting in discontinuation in 6 (3.4%): 3 men with gynecomastia and 1 man and 2 women with breast discomfort. Two of these patients discontinued spironolactone in the first 2 months and did not perform the second ABPM (Figure 1). One man (0.6%) interrupted spironolactone because of libido reduction. Biochemical abnormalities were observed in 5 patients (2.8%), in whom 4 (2.3%) required withdrawal of the drug: 2 patients because of acute worsening of renal function (serum creatinine level ≥ 177 μmol/L or doubling from baseline values) and 2 because of asymptomatic hyperkalemia (serum potas-

sium level >5.5 mmol/L); 1 patient (0.6%) had normalization of the serum potassium level after a decrease in spironolactone dosage.

Discussion

This prospective trial has some important findings. First, it confirms that spironolactone is effective in reducing office and ambulatory BPs in patients with true RH. As far as we know, this is the first study in which true RH was systematically established and followed-up by ABPM. Second, it demonstrates that spironolactone administration is relatively safe and that its BP lowering effect is persistent over at least a 15-month interval. Third, it shows that the presence of an increased waist circumference and a lower aortic stiffness

Table 3. Results of Multiple Linear Regression Analysis (Dependent Variable: Relative Percentage SBP Decrease During Spironolactone Administration)

Covariates	B Coefficient (SE)	Partial Correlation	P
Waist circumference, 5 cm	0.97 (0.38)	0.19	0.013
Aortic PWV, 1 m/s	−0.99 (0.44)	−0.17	0.026
Potassium, 1 mmol/L	−3.52 (1.73)	−0.15	0.044
Sex, 1=male; 2=female	1.79 (1.84)	0.08	0.33
Age, 1 y	0.02 (0.09)	0.02	0.78
No. of antihypertensive drugs	−0.87 (0.88)	−0.08	0.32

Table 4. Results of Multivariate Logistic Regression (Dependent Variable: Satisfactory [$>10\%$] SBP Response to Spironolactone)

Variables	Odds Ratio	95% CI	P
Waist circumference, 5-cm increment	1.20	1.03 to 1.41	0.019
Aortic PWV, 1-m/s decrement	1.23	1.03 to 1.47	0.021
Potassium, 1-mEq/L decrement	1.60	0.80 to 3.16	0.18
Sex, female	1.37	0.67 to 2.86	0.39
Age, 1-y increment	1.00	0.97 to 1.03	0.82
No. of antihypertensive drugs	1.00	0.77 to 1.54	0.60

reflected the predictors of higher BP reduction during spironolactone treatment, whereas neither PAC nor ARR influenced the BP response to spironolactone.

Many authors⁵⁻⁹ reported the impact of spironolactone in RH treatment, but none of them evaluated this effect on ambulatory BP. A prospective study⁸ evaluated office BP response to low-dose (12.5 to 50.0 mg) spironolactone in 76 resistant hypertensive patients taking an average of 4 antihypertensive drugs, all of them receiving a diuretic and a renin-angiotensin system inhibitor, and at the same time investigated hyperaldosteronism on the basis of a suppressed renin activity and high urinary aldosterone excretion. Similar to our results, spironolactone effect was considered additive to the use of diuretics (100% of our patients) and renin-angiotensin system inhibitors (94% of our patients), and the decrease of BP was similar in subjects with or without hyperaldosteronism (21 mm Hg in SBP and 10 mm Hg in DBP). There is only 1 survey¹⁰ that evaluated the effect of the addition of spironolactone on the basis of ambulatory BP as ours, but not specifically in RH. This study evaluated only 25 patients with uncontrolled hypertension (high BP despite the use of ≥ 2 other antihypertensive drugs) after a very short follow-up of only 1 month.

Other authors⁵⁻⁷ reported the impact of spironolactone in RH treatment, but the patient population was poorly characterized. The largest study, derived from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm,⁵ demonstrated a mean reduction of 22.0 mm Hg in the SBP and 9.5 mm Hg in the DBP in 1411 participants evaluated in whom low-dose spironolactone was introduced as a fourth drug. Nevertheless, patients originally from the amlodipine-perindopril-based regimen were not receiving diuretics in their therapeutic schemes, so they could probably not be considered resistant hypertensive patients.¹ Furthermore, in this study, only office BP was assessed. The only variables that appeared to weakly predict a better response were a lower baseline high-density lipoprotein cholesterol, a lower baseline serum potassium, and its rise during treatment. A retrospective study,⁶ in an uncontrolled hypertension population, also showed that a better response to spironolactone was correlated with lower baseline serum potassium levels. We also showed that serum potassium levels were independently and inversely correlated with the SBP response to spironolactone when analyzed as a continuous variable (Table 3) but not when the response was categorized (Table 4).

To discuss our findings related to aortic PWV measurements, it is opportune to emphasize that aldosterone and arterial stiffness are linked^{19,20} and that its effects on vasculature have already been reported.²¹ Arterial stiffness is an important determinant of systolic hypertension²² and an independent predictor of mortality in hypertensive patients.²³ Aldosterone is related to vascular damage, and its blockade has already been demonstrated to decrease aortic PWV.¹⁹ We did not evaluate the prospective effect of spironolactone on aortic PWV, and our results allow us only to affirm that spironolactone was more effective in decreasing SBP in patients with baseline lower aortic stiffness. The patients were enrolled from a large cohort of resistant hypertensive patients followed-up for ≤ 9 years¹²; hence, we suppose that

the better response occurred in those who had a smaller grade of established aortic wall fibrosis.²⁴

The link between elevated plasma aldosterone levels and the metabolic syndrome and its single components, especially abdominal obesity, although rather extensively evaluated, is still controversial.²⁵⁻²⁷ In spite of failing to reveal, as another study also did,⁸ any correlation between PAC or ARR and spironolactone response, we demonstrated that a higher waist circumference was one of the predictors of a greater SBP reduction after spironolactone use, thus supporting the relationship between obesity and potential aldosterone excess. Indeed, there is increasing evidence indicating the role of fat tissue, especially abdominal, as the main cause of increased aldosterone production in obesity. It was suggested that obesity-associated hypertension may be causally related to the accumulation of "dysfunctional" adipose tissue, which may induce activation of the sympathetic and renin-angiotensin-aldosterone systems and oxidative stress.²⁸ Interesting research about obesity and renin-independent stimulation of adrenal aldosterone secretion have been published, indicating that aldosterone secretagogues originating from adipocytes may be operative in overweight-obese patients.^{29,30} Similarly, visceral adipose tissue is thought to be a source of inflammatory adipokines that mediate systemic inflammation, oxidative stress, and insulin resistance.²⁵ Mineralocorticoid receptors on adipocytes promote inflammatory adipokine expression.³⁰ More recently, experimental studies have demonstrated, reciprocally, that mineralocorticoid receptor blockade reduced expression of these proinflammatory factors in adipose tissue and, at the same time, increased the expression of adiponectin, which has a potential protective effect against inflammatory adipokines.³¹ Whether these mechanisms are involved and how much they are important in RH have not been established yet. Additional studies are necessary to clarify whether aldosterone blockade in RH is more important in patients with abdominal obesity and metabolic syndrome, perhaps independent of traditional laboratory measurements of aldosterone excess.

We showed that spironolactone at low doses was safe and well tolerated, because only 11 patients (6.3%) stopped the drug during the follow-up because of adverse effects. In clinical practice, there is a reluctance to use spironolactone in men because of its estrogenic adverse effects.^{2,5} Actually, we included 48 male patients in our study, and 5 (10.5%) presented gynecomastia, 3 presented breast discomfort, and 1 presented libido reduction. One patient (with gynecomastia) was taking 100 mg of spironolactone, and the others were taking 50 mg/d. The rate of adverse effects observed in the present study was similar to that reported previously.^{2,5,9}

This study has some limitations that warrant discussion. The major one is that it is an open trial and not a randomized, blinded, placebo-controlled clinical trial. However, the difficulties, including ethical issues, of treating such high-risk resistant hypertensive patients with placebo are clear, and, as far as we know, such a clinical trial has never been performed nor is it being actually planned. Although this study enrolled the largest reported group of true resistant hypertensives, our sample size may have been small to detect some associations between BP response to spironolactone and patient baseline

characteristics. The absence of a correlation between measurements of aldosterone excess and spironolactone-induced BP reduction should be particularly faced with caution.

Perspectives

This open-label, prospective trial supports the use of low-dose spironolactone as a fourth or fifth drug in true RH management for decreasing office and ambulatory BPs, especially in those with abdominal obesity and lower aortic stiffness. Because we found no correlation between spironolactone response and laboratory measures of aldosterone excess, we suppose that aldosterone antagonism may play an important role in RH treatment independent of “aldosterone status” establishment. Otherwise, it can be argued that its effects in BP reduction may simply represent a better natriuretic action. Therefore, these findings and arguments provide a rationale for the designing of a large, multicenter, randomized double-blinded trial, with comparison of aldosterone-receptor blockade to another class of antihypertensive medication in RH. The comparison with other drugs commonly used as a fourth- or fifth-line drug, such as direct vasodilators, central α receptor agonists, or perhaps amiloride, can be used to confirm or refute the superior efficacy and safety of aldosterone receptor blockade in kidney and extrarenal tissues in patients with true RH.

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Disclosures

None.

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