Impact of Aldosterone Receptor Blockade Compared With Thiazide Therapy on Sympathetic Nervous System Function in Geriatric Hypertension

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Abstract—Aldosterone receptor blockade and thiazide therapy effectively lower blood pressure in geriatric hypertension. Their impact on sympathetic nervous system function has not been evaluated. In a double-blind, randomized study, 36 patients with stage 1 hypertension underwent 6 months of therapy with either aldosterone receptor blockade (spironolactone, n=19; 68±1 years) or hydrochlorothiazide (n=17; 68±2 years). Arterial blood pressure, [3H]-norepinephrine (NE) kinetics (extravascular NE release rate), and α-adrenergic responsiveness (forearm vasoconstriction to graded intrabrachial artery NE infusions) were evaluated at baseline, after a 4-week antihypertensive medication withdrawal, and after spironolactone or hydrochlorothiazide treatment. Arterial blood pressure decreased significantly with both spironolactone (160±3 to 134±2 mm Hg; 77±2 to 68±2 mm Hg) and hydrochlorothiazide (161±4 to 145±4 mm Hg; 78±2 to 73±2 mm Hg) treatment. Sympathetic nervous system activity was significantly reduced after spironolactone (plasma NE: 378±40 to 335±20 pg/mL, P=0.04; [3H]-NE release rate: 2.74±0.3 to 1.97±0.2 μg/min per meter squared, P=0.04) but not hydrochlorothiazide (plasma NE: 368±25 to 349±23 pg/mL, P=0.47; [3H]-NE release rate: 2.63±0.4 to 2.11±0.2 mg/min per meter squared, P=0.21). α-Adrenergic responsiveness was unchanged with either drug treatment. These findings demonstrate a beneficial effect of aldosterone receptor blockade on reducing sympathetic nervous system activity and blood pressure in hypertensive older patients. (Hypertension. 2010;55:1217-1223.)

Key Words: angiotensin ■ blood flow ■ hypertension ■ norepinephrine ■ sympathetic nervous system

For >50 years, thiazide diuretics have been the basis of antihypertensive therapy in the majority of placebo-controlled outcome trials, with proven efficacy in lowering blood pressure (BP) and a subsequent reduction in the incidence of many cardiovascular disease events.1 Even when compared with newer antihypertensive drug classes, results from studies such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial have prompted the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to endorse the thiazide drug class as first-line therapy for most hypertensive patients.2 This treatment approach continues despite the widely reported risks for adverse metabolic adverse effects, such as hypokalemia and insulin resistance, after long-term thiazide diuretic use.3

Attributed in part to these undesirable metabolic effects, the renin-angiotensin-aldosterone system has been intensively investigated as an alternate target for pharmacological intervention in the treatment of hypertension. Although angiotensin-converting enzyme (ACE) inhibitor therapy is equally effective as hydrochlorothiazide (HCTZ) in treating hypertension in older individuals, this treatment is not without some adverse effects. Indeed, this treatment modality is associated with aldosterone “escape” that may mitigate the beneficial effects of renin-angiotensin-aldosterone system blockade through a host of deleterious neurohumoral events.4 This finding has renewed interest in pharmacological targeting of other renin-angiotensin-aldosterone system components. One such alternative to ACE inhibition is aldosterone receptor blockade, which has proven efficacious in lowering BP to a similar degree as thiazide and ACE inhibitor monotherapy.5,6 In one of the few large-scale clinical trials of its kind, the Randomized Aldactone Evaluation Study7 reported a substantial reduction in morbidity and death for congestive heart failure patients treated with the aldosterone receptor blocker spironolactone (SPIRO) concurrent with ACE inhibitor therapy. Despite the promise of this drug class to improve patient outcomes, the mechanisms responsible for the antihypertensive action of aldosterone antagonism remain poorly understood.

With accumulating evidence for sympathetic nervous system (SNS) hyperactivity as a significant contributor to the pathogenesis and sequelae of essential hypertension,8 therapeutic approaches capable of reducing SNS activity are of particular clinical interest. In addition, given the well-described increase in SNS activity with advancing age,9-11 this may be

Received November 3, 2009; first decision November 29, 2009; revision accepted March 5, 2010.
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Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.109.147058

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even more pertinent for older hypertensive patients. In this regard, there is new evidence for the beneficial effects of aldosterone antagonism over thiazide therapy. A randomized crossover study in untreated hypertensive patients reported a significant increase in directly measured SNS activity after short-term chlorthalidone treatment but no SNS elevation after SPIRO therapy.12

On the basis of this background information, the focus of this investigation was to define the role for aldosterone receptor blockade therapy in geriatric hypertension, with a particular emphasis on its effects on the surrogate outcomes of neurohumoral abnormalities that characterize this population. We hypothesized that older hypertensive subjects treated with an aldosterone receptor blocker (SPIRO) would demonstrate a reduction in SNS activity, whereas SNS activity would remain unchanged with traditional thiazide diuretic treatment (HCTZ).

Methods

Subjects

Older subjects (>60 years) with stage 1 hypertension (seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) were recruited for the present study. All of the protocols were approved by institutional review board at the University of Michigan and the University of Utah, and written informed consent was obtained before participation in the study. Exclusion criteria included body mass index <19 or >40 kg/m2; use of medication that interferes with glucose metabolism or SNS function; evidence from screening laboratory evaluation of serious illness including (but not limited to) stage 3 hypertension (ie, diastolic BP ≥110 mm Hg and/or systolic BP >180 mm Hg); antiarrhythmic treatment with ≥2 drugs; orthostatic hypotension; renal insufficiency (serum creatinine >2.0 mg/dL); cognitive impairment (Folstein Mini-Mental State Examination <26); anemia; type 2 diabetes mellitus (ie, fasting plasma glucose ≥125 mg/dL or a glucose value >200 mg/dL at the 2-hour time point of a screening oral glucose tolerance test); contraindication to SPIRO or HCTZ; and evidence of secondary hypertension discovered by routine evaluation during the screening phase or other significant laboratory or resting ECG abnormalities.

Experimental Protocols

To minimize any effects of previous antihypertensive medications, all of the enrolled subjects discontinued antihypertensive medication for 4 weeks (an initial dosage taper with a 4-week medication-free period) before baseline measurements. After this medication washout period, subjects were randomly assigned to therapy with either SPIRO (25 mg daily) or HCTZ (12.5 mg daily). Subjects also received 0 (placebo), 20, or 40 mEq of KCl for blinded potassium supplementation as needed to maintain K+ >3.5 mEq/L. The dose of both drugs was titrated over 8 weeks to achieve a target BP of 140/85 mm Hg, achieved by 1 additional capsule of SPIRO (25.0 mg) or HCTZ (12.5) at 2-week intervals up to maximal doses of 100 and 50 mg, respectively. These maximal doses were chosen on the basis of the evidence that the efficacy of these agents to reduce BP plateaus at these doses13 and that their respective adverse effects become more common at higher doses. Subjects reported to the laboratory every 2 weeks for assessment of BP, evaluation of possible symptoms associated with the drug therapy, and determination of blood electrolytes. Subjects then continued on the dose of study medication achieved during the 8-week dose titration phase for the remainder of the 6-month treatment period. Subjects were advised not to deviate from their normal diet or physical activity routine during the course of the study.

Subjects reported to the General Clinical Research Center of the University of Michigan Medical Center at 7:30 AM to control for any diurnal variation in norepinephrine (NE) metabolism or arterial α-adrenergic tone. Subjects were instructed to fast from 10:00 PM the night before and to abstain from cigarettes, caffeine, and other known modulators of catecholamines for 12 hours before each study began. Subjects were studied in the supine position in a quiet room maintained at a constant temperature of 23°C to 25°C.

Forearm volume15 was measured using water displacement. A 20-gauge, 1.25-in Inspyre catheter was placed into the brachial artery of the nondominant arm. The catheter was connected to a pressure transducer (Hewlett-Packard 1290A quartz transducer; Hewlett-Packard). An intravenous catheter was placed in the contralateral arm for infusion of [3H]-NE. Beginning 30 minutes after insertion of the catheters, the [3H]-NE kinetics protocol was carried out as described previously15 with sampling from the brachial arterial catheter. Arterial samples were obtained for catecholamines levels every 10 minutes beginning 40 minutes into the infusion. Arterial BP was measured directly from the brachial artery, and heart rate was assessed by standard ECG.

Statistics were performed with the use of commercially available software (Sigma Stat 3.10, Systat Software Inc). Two-way repeated-measures ANOVA was used to identify between and within-group differences, with the Bonferroni test used for post hoc analysis when a significant main effect was found. All of the group data are expressed as mean±SE. Significance was established at P<0.05.

Measurements

Measurements of Body Composition

Total and abdominal body composition were assessed by dual energy X-ray absorptiometry (DXA; Lunar DPX-IQ 240 densitometer, medium collimation, medium speed, Lunar Radiation Corp) following the NE kinetics protocol. Analysis of DXA scans used Lunar software version 4.5c (extended research analysis). The percentage of total body fat was determined from the total fat mass divided by the body weight. The DXA measure of abdominal adiposity (DXA L1-L4) was determined with the manual analysis component of the Lunar software package, as described previously.16 Abdominal adiposity was measured as the fat mass within this region. The percentage of abdominal adiposity was determined from the DXA L1-L4 fat mass divided by total body fat mass.

SNS Activity

The protocol adapted for this analysis was based on our procedures published previously.15 The protocol consisted of an intravenous infusion of [3H]-NE, approximate specific activity 18.8 Ci/mmol (New England Nuclear), calculated to deliver 0.35 μCi/min per meter squared at a rate of 0.2 mL/min using an infusion pump. Ascorbic acid (1 mg/mL) was added to the infusion to prevent the oxidation of NE. The infusion was given for 1 hour to achieve a steady-state level of [3H]-NE. Arterial blood samples were taken from the brachial catheter at 40, 50, and 60 minutes during the infusion to determine arterial NE and [3H]-NE concentrations. The infusion was stopped at 1 hour, and additional arterial blood samples were collected at 1, 2, 4, 6, 8, 10, 14, 16, 18, and 20 minutes to measure [3H]-NE concentrations. Arterial NE levels were also obtained from the 10- and 20-minute decay time points. [3H]-NE concentrations were determined after alumina extraction of plasma (recovery ~60%) within 24 hours of the study. Liquid scintillation counting of the radiolabeled catecholamine was subsequently performed to determine [3H]-NE concentration.

The systemic NE kinetic parameters were derived using a 2-compartment model developed by Linares et al.17 This involved determining simultaneous fits of the tracee (arterial NE) and tracer ([3H]-NE) systems by the method of weighted nonlinear least squares. In this 2-compartment model, compartment 1 represents the vascular compartment and is, therefore, accessible to sampling. Compartment 2 represents the extravascular compartment into which NE is released from nerve terminals and exchanges with the vascular compartment and is, therefore, not accessible to sampling. The NE kinetic parameters estimated by this model included the following: (1) the rates of NE appearance into compartment 1 (in micrograms
per minute per meter squared) and into compartment 2 (NE\(_2\), in micrograms per minute per meter squared); (2) the metabolic clearance rate from compartment 1 (in liters per minute per meter squared); (3) the NE spillover fraction from compartment 2 to 1 (in percentages); and (4) the volume of distribution of NE in compartment 1 (in liters per meter squared). The values for NE\(_2\) were used as the primary indices of systemic SNS activity.

**\(\alpha\)-Adrenergic Responsiveness**

After the tracer \([^{3}H]\)-NE infusion protocol, forearm blood flow (FABF) was measured using venous occlusion plethysmography during an intra-arterial infusion protocol that we have described previously.\(^{15}\) To establish a stable baseline, FABF readings were taken until 3 consecutive readings representing similar FABF were obtained. To determine the effect of intra-arterial infusions of NE on FABF, NE (Levophed bitartrate, Sterling Drug) was diluted in 5% dextrose to achieve stepwise increasing infusion doses of 1.25, 5.00, 20.00, 80.00, and 240.00 ng ⋅ 100 mL of forearm value \(^{-1}\) ⋅ min \(^{-1}\).

Each NE dose was administered by an infusion pump (Harvard model 970T; Harvard Apparatus) for 4 minutes before FABF was recorded during the fifth minute of each infusion. After the FABF measurement at the 240-ng dose, the NE infusion was stopped.

**Plasma Catecholamine Analytic Methods**

Arterial blood samples were collected into chilled plastic tubes containing EGTA and reduced glutathione. The tubes were kept on ice until centrifugation at 4°C. Plasma samples were stored at \(-70°C\) until assayed. Plasma NE and epinephrine were quantified by a single-isotope radioenzymatic assay, with all of the samples from a given subject analyzed in the same assay. Alumina extraction of plasma samples and measurement of \([^{3}H]\)-NE levels were carried out as described previously.\(^{17}\)

### Results

Fifty-eight subjects were enrolled in the study after the screening evaluation and began a monitored 4-week antihypertensive drug withdrawal phase. In addition to a weekly visit to measure their BP, subjects were provided an automated ambulatory BP device (Omron) and instructed to report any systolic blood pressure values in excess of 180 mm Hg. Four subjects were not able to complete the drug washout phase because of BP elevations, and 2 were withdrawn when their BP values were normotensive after the drug washout. Forty three of the remaining 52 subjects agreed to the invasive arterial component of the study protocol, completed baseline studies, and were randomly assigned to either HCTZ or SPIRO. Seven subjects withdrew during the 6-month drug treatment, 2 for unspecified drug intolerance (1 from each group), 1 because of an intervening elective surgical procedure, and 4 for BP nonresponse (1 HCTZ and 3 SPIRO) defined a priori as an average SBP in excess of 160 mm Hg at the end of the dose-titration phase. Thus, results from 36 subjects who successfully completed the 6-month randomized treatment phase are presented. The mean achieved drug doses were 42±3 mg for HCTZ and 71±7 mg for SPIRO. There were no instances of hyperkalemia, and no other adverse effects were reported. Subjects randomized to HCTZ required an average KCl supplementation dose of 23±6 mEq/L. K\(^+\) values were constant throughout the 6-month treatment phase (HCTZ: 3.8±0.4 to 3.8±0.4 mEq/L; SPIRO: 4.1±0.2 to 4.2±0.3 mEq/L; both \(P\) values were not significant).

Subject characteristics are presented in Table 1. After a 4-week washout from prescribed hypertensive medication, resting arterial BP and heart rate were similar in the HCTZ and SPIRO treatment groups. In both HCTZ and SPIRO groups, arterial BP was significantly reduced after treatment (Figure 1), with no significant differences between drug groups. NE kinetics results are presented in Table 2. Treat-
Increased activation of the renin-angiotensin-aldosterone system in hypertension is well described. The roles of aldosterone in the development and progression of cardiovascular disease have been emphasized recently. Indeed, prospective analysis of the Framingham offspring study has identified serum plasma aldosterone levels in normotensive individuals as predictors for subsequent development of incident hypertension, and there is accumulating evidence for a causative role of aldosterone in the development of arterial hypertension and postmyocardial infarction sudden cardiac death. Although large-scale trials, such as the Randomized Aldactone Evaluation Study and the Eplerenone Post-Acute Myocardial Infarction Survival and Efficacy Study, have provided valuable proof of principle that mineralocorticoid receptor antagonism is of pathophysiologic importance in heart failure, much less is known regarding the effectiveness of this treatment modality in essential hypertension in the elderly.

Aldosterone receptor antagonists, such as SPIRO, promote sodium excretion and, thus, may reduce BP primarily by way of volume reduction. Several earlier studies demonstrated that SPIRO is an effective monotherapy for hypertension. In the present study, there were no reported cases of hypoten-
receptor blockade may not be attributed solely to diuretic effects. Rather, the efficacy of this drug treatment may involve preventing nervous system aldosterone receptor activation, which may, in turn, influence sympathetic outflow. Sympathoexcitation is present with advancing age and widely considered to play a significant role in the pathogenesis of essential hypertension, and, thus, this possible mechanism of action of SPIRO treatment is of significant clinical interest. This mechanism may be especially important among older hypertensive patients in whom systemic SNS activity tends to be further increased relative to normotensive age-matched individuals.

The NE kinetic parameter results summarized in Table 2 illustrate several important changes in SNS activity that were associated with 6 months of SPRIO therapy. In addition to the significant reduction in the rate of NE release into the extravascular compartment (NE2), the primary outcome measure of SNS activity in the present study, SPIRO therapy was also associated with significant reductions in NE mass estimates in both the vascular and extravascular compartments. These parameters were unchanged after HCTZ therapy. SPRIO therapy was also associated with a significant reduction in the NE volume of distribution and a corresponding reduction in its metabolic clearance rate. Plasma NE levels were significantly reduced after SPIRO therapy despite the drop in NE clearance rate, presumably because of the dominant reduction in NE compartmental mass.

To date few studies have been conducted to establish the effect of aldosterone receptor blocker therapy on SNS activity. In a recent study by Menon et al., muscle SNS activity was measured after both thiazide diuretic and aldosterone receptor antagonism in hypertensive patients. Using a 3-month crossover design without a washout period, this study identified sustained SNS stimulation during chlorthalidone but not SPIRO therapy, yet no change in baroreflex control of sympathetic nerve activity was observed after either drug treatment. The short duration of drug treatment, relatively young patient age (51 ± 2 years), and lack of information concerning associated changes in sympathetic end-organ (α-adrenergic) responsiveness after these treatment regimens limit generalization of the beneficial effects of aldosterone antagonism identified in this study to the geriatric hypertensive patient population. Building on this earlier work, the present study used a substantially longer treatment period with titrated drug doses; a noncrossover, randomized monotherapy approach; and an older cohort, with evaluation of both SNS activity and α-adrenergic responsiveness, to further identify the impacts of HCTZ and SPIRO in geriatric hypertensive patients. Each of these factors may partially explain discrepancies between the former and present findings, which together provide compelling evidence for the beneficial effects of SPIRO over thiazide diuretics with respect to SNS activation.

The current data extend earlier work in animals demonstrating the ability of aldosterone receptor blockade to decrease SNS activity in hypertensive and congestive heart failure mouse models. Although it is difficult to pinpoint the mechanisms responsible for the divergent effects of HCTZ and SPIRO in the present study, the lack of change in α-adrenergic responsiveness after HCTZ and SPIRO (Figure 3) suggests that the SPIRO-induced reduction in SNS activity may be attributable to a central inhibition of aldosterone receptors leading to a reduction in sympathetic outflow. This concept is supported by previous animal work demonstrating a discreet population of central mineralocorticoid receptors that, when blocked with SPIRO, potentiate sympathoexcitation. In contrast, human studies have failed to identify a change in arterial baroreflex control of arterial BP after chlorthalidone or SPIRO monotherapy. Alternately, the lack of change in α-adrenergic responsiveness could be because of combined upregulation in adrenoreceptor responsiveness opposed by reduced responsiveness from sodium depletion. However, we have demonstrated previously that the increase in arterial BP after acute sodium loading is not attributable to an increase in systemic SNS activity or increased arterial-adrenergic receptor responsiveness. Additional work is clearly needed to further examine which mechanisms are responsible for this sympathoinhibitory effect of SPIRO treatment in hypertensive humans.

Experimental Considerations

It is important to recognize that these results may not generalize to all older stage 1 hypertensive patients. These subjects were carefully screened to select a relative healthy
group with “simple” hypertension; namely, these subjects had normal renal function, were able to achieve BP control with a single agent, and did not have type 2 diabetes mellitus, known cardiovascular disorders, or other comorbid conditions. Although sleep disorders were not identified in inclusion/exclusion criteria, no patients enrolled in the present study were being treated for sleep apnea. Another potential limitation is that, although not statistically significantly different, the BP reduction achieved in the SPIRO group tended to be larger compared with HCTZ. Finally, it should be noted that, whereas the NE kinetic methodology used in this study provides an assessment of systemic SNS activity, potential regional differences in cardiac or renal SNS activity are not detected using this approach. This is an important distinction, because there is experimental evidence to indicate regional elevations in SNS activity in the absence of systemic changes in several experimental models of disease.30,31 However, there is no evidence supporting the converse, that is, that systemic elevations in SNS activity occur in the absence of regional changes. Thus, it seems probable that the measured decrease in systemic SNS activity after SPIRO in the present study should be accompanied by directionally similar changes in regional SNS activity.

Implications
Thiazide diuretics are often the first line of treatment in essential hypertension because of well-established BP-lowering effects, yet considerable metabolic adverse effects are experienced in many patients treated with this drug class. Likewise, inhibition of the ACE has proven BP-lowering action, yet this drug class also exhibits a number of adverse effects, including stimulation of prorenin/renin receptors. Indeed, “aldosterone escape” or “aldosterone breakthrough” is observed in ≈50% of patients receiving ACE inhibitor therapy,4 which has been associated with a number of clinical correlates, including elevated urinary albumin excretion,32 diminished maximal oxygen consumption,33 and a failure of treatment to improve left ventricular mass compared with nonescape patients.34 In the context of these clinically significant adverse drug effects, aldosterone receptor antagonism has emerged as an alternative antihypertensive treatment. Although not devoid of adverse effects,35 in patients with normal renal function and stable potassium and salt balance, this therapeutic approach may offer considerable advantage over other BP-lowering drug classes.

Perspectives
The present finding of a significant reduction in SNS activity after SPIRO treatment is of particular clinical significance considering the well-established deleterious effects of elevated SNS activity both in disease states and healthy aging.36 Indeed, even in the absence of overt cardiovascular disease, an age-related sympathoexcitation is present that may be associated with the age-related decline in peripheral blood flow,37 increased arterial thickening and associated reductions in arterial compliance,38 and reduced α-adrenergic39,40 and β-adrenergic41 responsiveness. The detrimental effects of SNS overactivity are even more profound in disease states such as advanced heart failure, where patients with the greatest sympathetic activation have the poorest survival.42 In the present study, the significant reduction in SNS activity after 6 months of aldosterone receptor blockade therapy was achieved without a change in end-organ (α-adrenergic) responsiveness, implicating a central mechanism for this change in autonomic activity. Although the exact mechanism by which this improvement is achieved remains unknown, the combined BP lowering and sympathoinhibitory action of SPIRO therapy lend valuable further support to the use of this drug class in the treatment of geriatric hypertension.

Acknowledgments
We thank Carol Mousigian, Cathie Stepien, Marla Smith, and the University of Michigan Clinical Research Center staff for their assistance with this investigation. In addition, we are grateful to the research volunteers without whom this study would not have been possible.

Sources of Funding
This study was funded in part by grants from the Veterans’ Affairs Medical Research Service (to M.A.S.), the Veterans’ Affairs Geriatric Research Education and Clinical Center, National Institute on Aging grant K07 AG 28403 (to M.A.S.), the Francis Family Foundation (Parker B. Francis Fellowship, to D.W.W.), the American Heart Association (grant 0835209N, to D.W.W.), and the University of Michigan Clinical Research Center grant M01-RR00042 (to M.A.S.).

Disclosures
None.

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