ORIGINAL PAPER

Racial Differences in Potassium Response to Spironolactone in Heart Failure

Evidence of racial differences in aldosterone concentrations and K^+ disposition suggests that response to aldosterone antagonism might vary by race. The authors sought to determine whether K^+ response to spironolactone differs between African Americans and Caucasians with heart failure. Heart failure patients of African-American (n=34) or Caucasian (n=17) race were started on spironolactone 12.5 mg/d, with up-titration as tolerated. Laboratory values and drug therapy were similar between racial groups at baseline. Spironolactone was titrated to a median dose of 25 mg/d in both groups. Neither concomitant medications nor serum creatinine changed significantly in either group during spironolactone dose titration. Median serum K^+ concentrations increased by 0.5 mEq/L (range, –0.7 to 1.6 mEq/L) in Caucasians, but only 0.1 mEq/L (range, –0.8 to 0.9 mEq/L) in African Americans; p<0.01. These data suggest that African Americans with heart failure may be less responsive to the renal effects of spironolactone. (CHF. 2006;12:200–205) ©2006 Le Jacq

The Randomized Aldactone Evaluation Study (RALES)[1] demonstrated significant reductions in morbidity and mortality with the addition of spironolactone to standard therapy in patients with severe heart failure (HF). Spironolactone attenuates the renal secretion of K^+, and serum K^+ concentrations commonly increase with spironolactone therapy. While the incidence of serious hyperkalemia with spironolactone was only 2% in RALES, a recent study suggests that spironolactone-induced hyperkalemia is much more common in HF patients outside the controlled clinical trial setting.[2] African Americans were underrepresented in RALES. Thus, the safety of spironolactone in African Americans with HF has not been well established. Evidence of racial difference in aldosterone concentrations and K^+ disposition suggests that K^+ response to aldosterone blockade with spironolactone may vary by race.[3–7]

In a previous retrospective analysis of patients receiving spironolactone for HF in addition to an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), we found that spironolactone use was associated with significantly lower serum K^+ concentrations in African Americans compared with Caucasians.[8] The lower K^+ concentrations in African Americans occurred despite higher doses of ACE inhibitors and a higher frequency of K^+ supplementation in this racial group. These data suggested that race may be an important determinant of K^+ response to spironolactone. However, given the retrospective nature of the earlier study, we were unable to directly analyze changes in K^+ with the addition of spironolactone. In particular, we were unable to exclude racial differences in baseline K^+ concentrations as an explanation for our findings. Thus, we designed the current study to determine whether there are racial differences in K^+ response to spironolactone by prospectively comparing the effects of spironolactone on K^+ concentrations between African Americans and Caucasians with HF.

Methods

Patients. Adult patients of African-American or Caucasian race were enrolled from the HF clinics at the University of Illinois at Chicago and the Evanston Northwestern Medical Center in Evanston, IL, before the initiation of spironolactone. Race was based on self-report. Additional inclusion criteria

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were a left ventricular ejection fraction ≤40% by echocardiography or multigated radionuclide angiography within the previous 6 months and treatment with optimal doses of ACE inhibitors or ARBs. Optimal doses were defined as either the doses associated with reductions in morbidity and mortality in clinical trials or maximally tolerated doses.[9] Exclusion criteria were serum K^+ concentration ≥5.0 mEq/L, serum creatinine ≥2.5 mg/dL, and treatment with spironolactone or eplerenone within the previous 12 months. This study was approved by the Institutional Review Board at each location.

Study Procedures. Once the clinical decision to start spironolactone was made, and after obtaining written informed consent, blood was collected for baseline serum K^+, creatinine, and aldosterone concentrations. All baseline blood samples were collected between 8 a.m. and noon while patients were seated with their legs dangling (upright position). If serum K^+ was <5.0 mEq/L and serum creatinine was <2.5 mg/dL, spironolactone was started at a dose of 12.5 mg/d. Patients were asked to return to the laboratory in 1 week for repeat blood chemistry. If K^+ remained <5.0 mEq/L and creatinine remained <2.5 mg/dL, spironolactone was increased to 25 mg/d. Further increases in the spironolactone dose and changes in K^+ supplementation were made at the discretion of the treating clinician. Patients were asked to return to the laboratory 1 week after spironolactone dose titration for reassessment of serum K^+ and creatinine. Spironolactone tablets were provided by members of the research team.

We collected data on demographics, medical history, concomitant medications, New York Heart Association (NYHA) functional class, and left ventricular systolic function as assessed by the most recent echocardiogram or multigated radionuclide angiography. At the time of each laboratory visit, patients were questioned about adherence to spironolactone and any changes in medications.

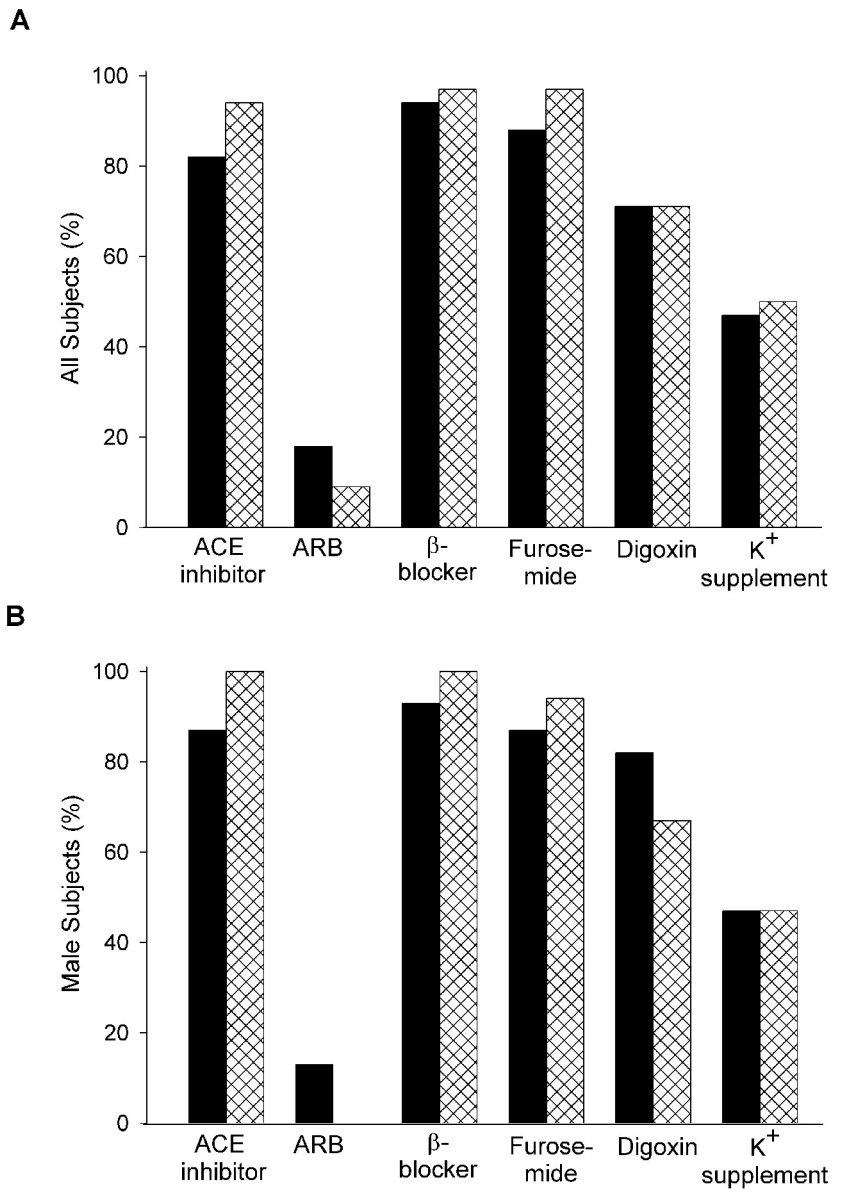

Figure 1. Percentages of (A) all patients and (B) male patients taking various classes of heart failure medications. Solid bars=Caucasians; hatched bars=African Americans; ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker

Laboratory Analyses. Serum samples for aldosterone were stored at –70°C until analysis. Aldosterone concentrations were determined in duplicate by radioimmunoassay using a commercially available kit containing iodine-125-labeled aldosterone (Diagnostic Systems Laboratories, Inc., Webster, TX) according to kit instructions. Intra-assay and interassay coefficients of variation with this assay were 1.5% and 1.9%, respectively. Serum K^+ and creatinine concentrations were determined in the clinical laboratory at each institution.

Statistical Analyses. Patient characteristics and laboratory values were summarized as median (range) for continuous data and as percentages for categoric data. Characteristics were compared between African Americans and Caucasians by the Pearson's χ^2 analysis or the Fisher exact test where

Table. Baseline Characteristics of Study Patients

Characteristic	African Americans		Caucasians		*p* Value	
	Total	Men	Total	Men	Total	Men
Number	34	17	17	15	—	<0.01
Age (yr)	48 (21–75)	48 (24–75)	64 (37–88)	64 (43–88)	<0.01	<0.01
Body mass index (kg/m^2)	32 (20–92)*	32 (20–92)*	29 (23–40)	28 (23–40)	0.09	0.15
NYHA functional class	III (I–IV)	III (I–III)	III (II–IV)	III (II–IV)	0.13	0.09
Medical history (%)						
Ischemic heart disease	15	18	65	67	<0.01	<0.01
Hypertension	79	76	47	47	<0.05	0.08
Diabetes mellitus	24	24	65	60	<0.01	<0.05
K^+ (mEq/L)	4.3 (3.5–4.9)	4.2 (3.6–4.9)	4.3 (3.3–4.9)	4.3 (3.3–4.9)	0.98	0.92
Creatinine (mg/dL)	1.3 (0.7–2.3)	1.3 (0.7–2.0)	1.2 (0.8–2.1)	1.2 (1.0–2.1)	0.79	0.97
Creatinine clearance (mL/min)	60 (22–154)	62 (42–154)	61 (22–94)	61 (22–94)	0.81	0.22
Aldosterone (pmol/L)	280 (49–823)	258 (107–823)	224 (148–1056)	224 (148–1056)	0.83	0.96
Daily drug doses						
Enalapril/lisinopril (mg)	40 (10–40)	40 (10–40)	30 (7.5–40)	30 (7.5–40)	0.18	0.17
Furosemide (mg)	100 (20–320)	100 (20–320)	80 (20–300)	80 (20–300)	0.57	0.64
Metoprolol (mg)	150 (25–400)	100 (25–200)	50 (25–150)	75 (25–150)	0.05	0.31
K^+ supplement (mEq)	20 (16–60)	20 (20–40)	30 (20–60)	20 (20–60)	0.53	0.69

Data are presented as median (range) or %. NYHA=New York Heart Association; *one patient weighed 274 kg

appropriate for nominal data and the Mann-Whitney *U* test for continuous data. Changes in K^+ concentrations from baseline with spironolactone were analyzed within each racial group using the Wilcoxon signed ranks test.

Results

A total of 34 African Americans and 17 Caucasians were enrolled. The median age of the study participants was 54 years, and 63% were women. Baseline characteristics of African-American and Caucasian patients are shown in the Table. All but two Caucasians, but only 17 African Americans, were men; $p<0.01$. Therefore, we present data for the total study population and for men only. African Americans were younger, more likely to have hypertension, and less likely to have a history of ischemic heart disease or diabetes. Baseline laboratory values and the severity of HF were similar between racial groups; the majority of patients (67%) had NYHA class III or IV HF. Given the age difference between groups, creatinine clearance was calculated using the equation of Cockroft and Gault with ideal body weight to provide a better estimation of renal function.[10] Calculated creatinine clearance was similar between groups.

Information about HF drug therapy at baseline is depicted in Figure 1 and the Table. Ninety percent of all patients were taking an ACE inhibitor, with the remaining patients taking an ARB. One African American was taking both classes of drugs concurrently. Enalapril and lisinopril were the most commonly prescribed ACE inhibitors, accounting for 91% of ACE inhibitors used by study participants. The doses of enalapril and lisinopril, which were combined because they are generally considered dose equivalents, were similar between groups. Beta-blocker use was high in both groups (>90%), and the majority (69%) of β-blocker–treated patients were taking metoprolol. The dose of metoprolol tended to be higher in African Americans compared with Caucasians ($p=0.05$). Furosemide was the only loop diuretic used. One patient in each group was taking furosemide and a thiazide diuretic concomitantly. Nearly half of the patients in each group were taking a K^+ supplement at baseline.

Considering the population as a whole (both men and women), spironolactone was titrated to a median (range) dose of 25 mg/d (12.5–37.5 mg/d) in both racial groups. One African American and no Caucasians reported missing one or more doses of spironolactone during the study period. There were no significant changes in concomitant HF medications or K^+ supplementation in either group during spironolactone dose titration. Figure 2 illustrates changes in serum creatinine and K^+ from baseline with titration of spironolactone. Serum creatinine did not change significantly in either group. While serum K^+ remained unchanged in African Americans, it increased significantly ($p=0.004$) in Caucasians. The median (range) increase in K^+ was 0.1 (–0.8 to 0.9) mEq/L in African Americans and 0.5 (–0.7 to 1.6) mEq/L in Caucasians ($p<0.01$). Similar results were observed among male patients, with significantly greater K^+ increases in Caucasians vs. African Americans. A complementary analysis of variance showed that the association between race and K^+ changes with spironolactone remained significant ($p=0.002$) in the presence of diabetes, while no significant interaction between diabetes condition and race was observed.

Serum K^+ concentration exceeded 5.0 mEq/L with spironolactone therapy in three (8%) African Americans, one of whom was on K^+ supplements. These African-American patients had a median (range) baseline serum creatinine of 2.1 (2.0–2.3) mg/dL and a calculated creatinine clearance of 23 (22–48) mL/min. Seven (41%) Caucasians, three of whom were on K^+ supplements, had a serum K^+ level >5.0 mEq/dL with spironolactone ($p<0.01$ compared with African Americans). Baseline serum creatinine and creatinine clearance were 1.2 (1.0–2.1) mg/dL and 60 (22–94) mL/min, respectively, in these Caucasian patients. Only one patient, a Caucasian man, developed hyperkalemia, defined as a K^+ level >5.5 mEq/L. This patient had a baseline serum creatinine of 2.1 mg/dL and a creatinine clearance of 22 mL/min. Potassium returned to normal in this patient after the discontinuation of K^+ supplements.

Discussion

We found that Caucasians, but not African Americans, had significant increases in serum K^+ with the addition of spironolactone to standard HF therapy. The interracial difference in K^+ response occurred despite similar renal function and diuretic and vasodilator therapy between groups. While sex distribution differed between racial groups, we do not believe that this influenced our results, since the racial difference in K^+ response to spironolactone persisted when we limited our analysis to men.

A recent study found significant increases in hospital admissions for hyperkalemia and hyperkalemia-associated mortality accompanying the rise in spironolactone use following the publication of RALES.[2] Information about the racial background of patients in that study was unavailable.[11] Our findings suggest that African Americans are at lower risk for hyperkalemia with aldosterone antagonists compared with Caucasians.

The majority of our patients on K^+ supplements at baseline were continued on supplements when spironolactone was started. However, only one patient developed hyperkalemia, and none of our study participants required interventions to correct K^+, other than discontinuing spironolactone or K^+ supplements. This is possibly because spironolactone was started at a dose of only 12.5 mg/d, with up-titration as tolerated. Serum K^+ concentration exceeded 5.0 mEq/L in three of the eight Caucasians on K^+ supplements. These data emphasize the importance of discontinuing, or at least reducing, K^+ supplementation before starting spironolactone in Caucasian patients. Given that several Caucasians with a K^+ level >5.0 mEq/L had normal renal function, our data further suggest that continuation of K^+ supplements with spironolactone is risky in Caucasians, regardless of renal function. Only one of the 12 African Americans who remained on K^+ supplements had a serum K^+ concentration >5.0 mEq/L with spironolactone, and none developed hyperkalemia. In addition, baseline serum creatinine was ≥2.0 mg/dL in all three African Americans with a K^+ level >5.0 mEq/L. Thus, our findings also suggest that stopping K^+ supplements before starting spironolactone may be less important in African Americans unless serum creatinine is elevated.

The mechanism underlying possible racial differences in K^+ response to spironolactone is unclear. While there are reports of lower aldosterone concentrations and aldosterone excretion rates among children as well as patients with hypertension of African-American compared with Caucasian race, baseline aldosterone concentrations,

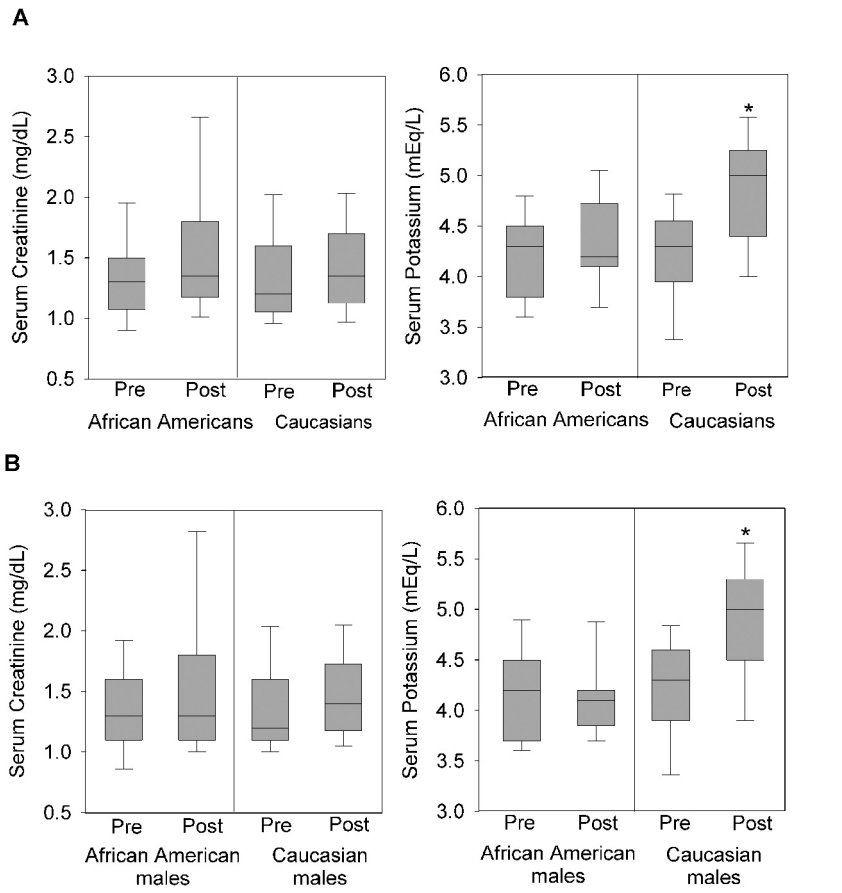

Figure 2. Median and percentile ranges for serum creatinine and K^+ concentrations at baseline (Pre) and after maximum spironolactone dose titration (Post) for (A) all patients and (B) male patients only. Lines within boxes represent medians. The lower and upper boundaries of the boxes mark the 25th and 75th percentiles, and the whiskers below and above the boxes indicate the 10th and 90th percentiles. *$p=0.004$ for change in serum K^+ in Caucasians

measured in the upright position, were similar between racial groups in our study.[4–6] Thus, our findings do not appear to be attributable to racial differences in baseline aldosterone levels. Aldosterone exerts its effects through stimulation of the mineralocorticoid receptor, and spironolactone competitively inhibits aldosterone binding to this receptor. Hence, one possible theory to explain racial differences in spironolactone response despite similar aldosterone concentrations is that the activity of the mineralocorticoid receptor may vary by race.

Alternatively, racial differences in K^+ response may be due to variability in the activity of Na^+/K^+-activated adenosine triphosphatase (Na^+/K^+-ATPase), which catalyzes the movement of K^+ into renal tubule cells in exchange for Na^+. Indeed, previous investigators have reported lower Na^+/K^+-ATPase activity in red blood cells from African Americans compared with Caucasians.[12,13] There is also evidence supporting lower Na^+/K^+-ATPase activity in skeletal muscle cells in African Americans.[3] The Na^+/K^+-ATPase pump system in the renal tubule cell is dependent on aldosterone.[14] Thus, lower basal Na^+/K^+-ATPase activity and, hence, lesser K^+ secretion into the renal tubule cell in African Americans, may result in smaller K^+ responses to aldosterone antagonism in this racial group.

African Americans in our study had a higher prevalence of hypertension and a lower prevalence of ischemic heart disease compared with Caucasians. Our findings in regard to racial differences in the putative etiology of HF are consistent with those of previous studies.[15–18] The renin-angiotensin-aldosterone system is activated in response to a decline in the pumping capacity of the heart, regardless of the nature of the inciting event.[19] As such, it would be expected that aldosterone antagonists would provide similar benefits in patients who have HF secondary to either an ischemic or nonischemic cause. In RALES, nearly half of study participants receiving spironolactone had a nonischemic cause for their HF, whereas 100% of participants in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[20] had ischemic heart diease.[1,20] Aldosterone antagonism provided similar benefits and similar increases in serum K^+ (median increase of 0.30 mEq/L) in both study populations. Based on this evidence, we do not believe that racial differences in the prevalence of hypertension and ischemic heart disease affected our results.

Our findings are potentially confounded by differences in age and diabetes prevalence between groups. We would expect age to primarily affect renal function, and creatinine clearance (which takes age into account) was similar between groups. Thus, we do not believe that age differences affected our results. More Caucasians compared with African Americans had diabetes. Insulin deficiency in patients with diabetes increases the risk for hyperkalemia by impairing the intracellular shift of K^+.[21] In addition, diabetic nephropathy is a common cause of hyporeninemic hypoaldosteronism, which increases the risk for hyperkalemia with aldosterone antagonists.[14] However, the inclusion of diabetes in our analysis of variance did not alter the magnitude of the effect of race on K^+ response to spironolactone, suggesting that racial differences in diabetes prevalence did not influence our results.

The median increase in K^+ concentration was 0.3 mEq/L in RALES, in which the majority (>85%) of participants were Caucasian. The median K^+ increase was 0.5 mEq/L among Caucasian patients in our study. The greater increase in K^+ in our study compared with RALES is likely secondary to higher ACE-inhibitor doses and a greater use of β blockers among our study patients. Specifically, ACE-inhibitor doses were over twice as high in our study compared with RALES. In addition, 96% of our study participants vs. only 11% of RALES participants were taking a β blocker. There is evidence that β blockers may interfere with the cellular uptake of K^+, thus potentiating the risk for hyperkalemia with spironolactone.[22]

Limitations. There are some limitations of our findings that should be discussed. First of all, we did not assess dietary K^+ intake, and there is evidence that African Americans consume less K^+ than Caucasians, which likely contributes to the higher prevalence of unprovoked hypokalemia in this racial group.[23] Thus, we cannot exclude dietary differences between groups as a contributor to our results. However, baseline K^+ concentrations were similar between groups, suggesting that any racial differences in dietary K^+ intake before the start of spironolactone were corrected through the use of K^+ supplements. Secondly, adherence to spironolactone therapy was assessed through interview, and was thus dependent on patient recall. In addition, we did not assess adherence to diuretic therapy and vasodilator therapy, both of which influence serum K^+ concentrations.

Summary

Our study showed that Caucasians have significant increases in serum K^+ with spironolactone therapy, whereas there are minimal changes in K^+ concentrations with spironolactone use in African Americans. Our findings suggest that African Americans are less responsive to the renal effects of spironolactone compared with Caucasians. This may have important implications for the management of K^+ supplementation and the intensity of K^+ monitoring with spironolactone therapy. Whether the cardiac effects or clinical outcomes with spironolactone vary by race remains to be examined.

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