Renin-Angiotensin-Aldosterone System

Mechanisms of Impaired Potassium Handling With Dual Renin-Angiotensin-Aldosterone Blockade in Chronic Kidney Disease

Richard A. Preston, David Afshartous, Dyal Garg, Sergio Medrano, Alberto B. Alonso, Rolando Rodriguez

Abstract—The combination of an aldosterone receptor antagonist added to an angiotensin-converting enzyme inhibitor has been demonstrated to reduce cardiovascular and renal end points in hypertensive humans but can produce hyperkalemia in the common clinical setting of impaired renal function. We investigated the effects of dual therapy on acute and chronic potassium handling in hypertensive humans with renal impairment by conducting a randomized crossover clinical trial of 4 weeks of 40 mg lisinopril/25 mg spironolactone versus placebo in 18 participants with a glomerular filtration rate of 25 to 65 mL/min. Study end points, following an established protocol, were hourly determinations of dynamic renal potassium excretion (mmol/h) and serum potassium (mmol/L) after 35 mmol oral potassium challenge in addition to ambulatory potassium concentration. After 4 weeks, ambulatory potassium concentration was 4.87 mmol/L with lisinopril/spironolactone versus 4.37 with placebo (P<0.001). Lisinopril/spironolactone produced only a modest 0.44 mmol/h reduction in stimulated potassium excretion (P=0.03) but a substantial 0.67 mmol/L increase in serum potassium (P<0.001) in response to 35 mmol potassium; these findings are consistent with impaired extrarenal/transcellular potassium disposition. We found the increase in serum potassium after an oral potassium challenge to be a strong predictor of the increase in ambulatory potassium with lisinopril/spironolactone. Our study suggests that dual renin-angiotensin-aldosterone blockade may impair extrarenal/transcellular potassium disposition in addition to reducing potassium excretion in humans with renal impairment, and that acute changes in dynamic potassium handling are predictive of chronic changes in ambulatory potassium concentration with dual renin-angiotensin-aldosterone blockade. (Hypertension. 2009;53:754-760.)

Key Words: potassium ■ hyperkalemia ■ renal insufficiency ■ chronic ■ aldosterone antagonists ■ angiotensin-converting enzyme inhibitors ■ renin-angiotensin-aldosterone system

Aldosterone has been implicated recently as a key mediator of progressive cardiovascular and renal disease,1–2 and consequently, there has been intense interest in aldosterone blockade as an effective new treatment strategy.1–8 Randomized clinical trials have demonstrated that dual blockade of the renin-angiotensin-aldosterone system (RAAS) with an aldosterone antagonist added to either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker can substantially reduce cardiovascular end points in high-risk patients.1–4 Further, there is accumulating evidence that dual RAAS blockade can ameliorate the progression of chronic kidney disease (CKD).1,5–8

Unfortunately, drugs that block the RAAS can impair renal potassium handling and dual RAAS blockade can potentially produce or exacerbate hyperkalemia, especially among those patients with CKD.9–12 On the other hand, clinical trial data suggest that hyperkalemia is relatively uncommon overall with dual RAAS blockade. The majority of patients with CKD tolerate dual RAAS blockade without developing hyperkalemia and should therefore be offered the opportunity of a potentially beneficial therapy.1–8 In addition to careful adherence to specific safety criteria,1,3,4 innovative methods to predict the quantitative effects of dual RAAS blockade on the ambulatory serum potassium (ambulatory SEK) concentration in patients with CKD and renal functional impairment could augment individualized prescription of dual RAAS blockade and substantially reduce the risk of hyperkalemia.

We propose that investigation of the quantitative effects of dual RAAS blockade on dynamic renal potassium handling using an established protocol13–15 in study participants with CKD can provide useful insight into the mechanisms producing impaired potassium handling. At present, the quantitative effects of dual RAAS blockade on dynamic renal potassium handling in patients with renal impairment have not been investigated.
The specific objectives of this placebo-controlled randomized crossover clinical trial are to: (1) compare the mechanisms of dynamic renal potassium handling in study participants with CKD and an estimated glomerular filtration rate (GFR) of 25 to 65 mL/min versus control participants with normal GFR; (2) compare the effects of 4 weeks of dual RAAS blockade with 40 mg lisinopril and 25 mg spironolactone versus placebo on dynamic renal potassium handling and ambulatory SEK in participants with CKD; (3) investigate the mechanisms of impaired renal potassium handling induced by dual RAAS blockade; and (4) using a mixed-effects models approach, investigate the predictive relationship between acute dynamic renal potassium handling variables and the corresponding changes in ambulatory SEK during 4 weeks of dual RAAS blockade.

Methods

This study was a randomized, placebo-controlled, 2-treatment crossover clinical trial to determine the effects of 4 weeks of dual RAAS blockade with 40 mg lisinopril daily and 25 mg spironolactone daily versus placebo on dynamic renal potassium handling and ambulatory SEK in 18 participants with CKD and modification of diet in renal disease (MDRD) equation estimated GFR 25 to 65 mL/min. Eighteen gender-matched participants with estimated GFR >100 mL/min who received no study medication underwent a single potassium handling study to provide a comparison group. Our protocol for potassium handling uses a conservative 35-mmol oral potassium challenge followed by hourly determinations of creatinine-adjusted urinary potassium excretion (aUkV; mmol/h), dynamic serum potassium concentration (dynamic K; mmol/L), and fractional excretion of potassium (FEK).

The primary study end point was aUkV (mmol/h) at hours 2 and 3 after an oral 35-mmol potassium challenge. Secondary end points were ambulatory SEK at the beginning and end of each 4-week treatment period and dynamic changes in K and FEK. We used aUkV because the accuracy of timed urine collections can be limited by a residual volume of urine after each timed void because of incomplete emptying of the bladder. aUkV helps to account for potential bias created by these residual bladder urine volumes.

Study Participants

This study was performed in accordance with the Declaration of Helsinki and was approved by the University of Miami Human research subjects committee (institutional review committee). Written informed consent was obtained directly from all participants before entry into the study and before any study procedures. Participants with CKD were 20 to 80 years of age with an estimated GFR of 25 to 65 mL/min who received no study medication. ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, diuretics, and other drugs that could alter potassium balance were stopped/tapered. β-Blockers prescribed specifically for the indication of coronary heart disease were continued throughout all phases of the study, including both potassium-handling protocols at the same dosage. (2) Treatment period 1: 4-week randomized treatment with either placebo or 40 mg lisinopril/25 mg spironolactone. Blood pressure and ambulatory SEK concentration were determined at each weekly study visit. (3) 3-day inpatient confinement period 1 for diet stabilization concluded by a potassium handling study. (4) 2-week washout period on no study medication. (5) Treatment period 2: 4-week randomized treatment with the crossover treatment. (6) 3-day inpatient confinement period 2 for diet stabilization concluded by a potassium handling study.

Inpatient Confinement Period and Renal Potassium Handling Study

At the final visit of each 4-week treatment period, participants were admitted to the inpatient clinical pharmacology unit, where they received a diet containing 100 mmol Na and 50 mmol K for 2 days. In patients with diabetes mellitus receiving insulin, the insulin was held until after the potassium handling study and then administered with a full meal.

On the third day after an overnight fast, 2 successive 500-mL oral water loads were followed directly by a 2-hour baseline urine collection. After the 2-hour baseline collection period, a potassium load of 35 mmol (as 20% potassium chloride) was administered in 240 mL of ginger ale over 5 to 10 minutes. Urine was collected thereafter for 5 additional 1-hour periods and analyzed for potassium and creatinine. Water (300 mL) was given at the midpoint of each hourly collection period to maintain urine flow.

Blood was drawn at the midpoint of the 2-hour baseline period and at the midpoint of each 1-hour experimental period and analyzed for potassium and creatinine. Aldosterone and insulin were determined for comparison between control subjects and subjects with CKD. Aldosterone was determined at baseline, hour 3, and hour 5. Insulin was determined at baseline and hour 3. A low-potassium snack was provided immediately after the hour-3 blood draw. A 12-lead ECG was performed at baseline and at hour 3 to identify changes suggestive of hyperkalemia.

Insulin and Aldosterone

Aldosterone (ng/mL) was determined by a competitive binding immunoassay (Quest Diagnostics). Insulin (μU/mL) was determined by a 2-site sandwich immunoassay (ADVIA) using direct chemiluminescent technology.

Statistical Methods

Standard Statistical Methods

Assuming an SD of 1 mmol/h in aUkV at hour 3, a sample size of 14 study participants was calculated to detect a reduction in mean hour 3 aUkV of 1 mmol/h with power 0.80 and α=0.05. Differences in aUkV, FEK, and dynamic K at hours 2 and 3 and changes in ambulatory SEK during dual RAAS blockade versus placebo were assessed via paired t tests and confirmed via nonparametric bootstrap t tests.

Comparison of aUkV Versus Time Curves Using Mixed-Effects Models

In addition to standard t tests, we applied a mixed-effects model statistical approach detailed previously to investigate drug-induced delays in reaching maximal aUkV, blunting of aUkV, and shift/separation in aUkV curves at maximum aUkV.
Mixed-Effects Model Approach to Investigate the Predictive Relationship Between Dynamic Potassium Handling Variables aUkV and Dynamic K and Changes in Ambulatory SEK With Dual RAAS Blockade

A linear mixed-effects modeling approach was used to predict drug-induced changes in ambulatory SEK concentration from dynamic potassium handling variables aUkV, dynamic K, and MDRD-estimated GFR with indicator variables for dual blockade to assess the differential impact of drug treatment on ambulatory SEK. Model estimation was performed via maximum likelihood in the nlme package of R.20-22 and a series of models were assessed via t tests were used to test hypotheses regarding the fixed effects in the model. Formally, the final model is displayed below (subject index i = 1,…,18; time index j = 1,…,5; drug index k = 1,2).

\[ Y_{ij} = \left( \gamma_{10} + \gamma_{11}Drug_{1} + \gamma_{12}Drug_{2} + \gamma_{13}Drug_{1} \times \Delta K + \gamma_{14}Drug_{2} \times \Delta aUkV \right) 
+ \left( \gamma_{20} + \gamma_{21}Drug_{1} + \gamma_{22}Drug_{2} + \gamma_{23}Drug_{1} \times \Delta aUkV + \mu_{1i} + \mu_{2i} \times \Delta K + \gamma_{24}Drug_{2} \times \Delta aUkV \right) 
+ \gamma_{40}MDRD + e_{ij} \]

where \( e_{ij} \) is the normally distributed within-subject error term with zero mean and variance \( \sigma^2 \), and \( \mu_{1i} \) and \( \mu_{2i} \) are normally distributed between-subject random effects with zero mean, covariance \( \tau_{12} \), and variances \( \tau_{1} \) and \( \tau_{2} \), respectively, and \( \Delta aUkV \) and \( \Delta K \) represent the hour 2 and hour 3 changes from baseline of aUkV and dynamic K, respectively. The first 4 time points correspond to the 4 weekly visits, and the last time point corresponds to the baseline (hour zero) of the dynamic excretion data.

Results

Baseline and Demographic Characteristics

Nineteen of 31 potential study participants met eligibility criteria and were enrolled into the study. One participant was withdrawn because of hyperkalemia while receiving placebo. Baseline and demographic characteristics of the 18 participants who completed all phases of the study are shown in Table 1 compared with 18 gender-matched control participants. Control participants were younger than the participants with CKD. Both groups were predominantly composed of Hispanic men.

Comparison of Dynamic Renal Potassium Handling in Participants With CKD Versus Control Participants With Normal Renal Function

Participants with CKD demonstrated markedly suppressed potassium excretion compared with control participants (Figure 1A). Mean aUkV after a 35-mmol potassium challenge at hours 2 and 3 were 3.75 mmol/h and 3.92 mmol/h, respectively, in participants with renal impairment compared with 10.3 mmol/h and 8.2 mmol/h in control participants. There was a large difference in the total amount of potassium excreted during the 5-hour collection period. The control group was able to eliminate 33.55 of the 35 mmol by renal excretion, whereas the CKD group eliminated only 15.98 (P<0.001). The reduced aUkV in the CKD group was associated with a higher FEK at baseline and hours 3, 4, and 5 compared with control subjects (Figure 1B). Peak FEK was similar in both groups at hour 2.

Serum potassium concentration (mmol/L) for participants with renal impairment receiving placebo was similar to control participants at baseline (4.37 versus 4.49; P=0.25), hour 2 (4.72 versus 4.77; P=0.4), and hour 3 (4.66 versus 4.52; P=0.8). Participants with CKD were therefore able to maintain serum potassium concentration in the same range as control subjects at baseline and after a 35-mmol challenge despite a marked reduction in potassium excretion. Together, these observations are consistent with a substantial increase in extrarenal potassium disposition in CKD such as cellular translocation or possibly gastrointestinal secretion/malabsorption.

Aldosterone concentration at baseline and in response to an oral potassium challenge was reduced in participants with renal impairment compared with control subjects (please see online supplement available at http://hyper.ahajournals.org). Peak hour 3 aldosterone was 17.5 ng/mL in healthy control subjects (P=0.09).
Effects of Dual RAAS Blockade Versus Placebo on Blood Pressure and Ambulatory SEK Concentration During 4-Week Outpatient Treatment Periods

After 4 weeks of treatment, mean systolic pressure was 135 mm Hg with placebo and 123 mm Hg with dual RAAS blockade ($P=0.006$). Diastolic pressure was 80 mm Hg versus 75 mm Hg ($P=0.013$).

Participants with renal impairment demonstrated a sustained increase in ambulatory SEK concentration within 1 week of commencing dual RAAS blockade (Figure 2). This increase was further amplified by 2 days of 50 mmol per day dietary potassium during inpatient confinement: mean ambulatory SEK concentration with dual RAAS was 4.87 mmol/L compared with 4.42 mmol/L for placebo ($P<0.001$). Body weight did not differ between placebo and dual RAAS blockade ($P=0.3$).

Effects of Dual RAAS Blockade on Dynamic Renal Potassium Handling: aUkV, FEK, and Dynamic K

**Dynamic aUkV**

As described, aUkV was markedly impaired in participants with CKD receiving placebo compared with control participants. Dual RAAS blockade with lisinopril and spironolactone produced a statistically significant but modest reduction in aUkV compared with placebo (Figure 3A). Mean aUkV at hour 2 was reduced from 3.75 mmol/h on placebo to 3.31 mmol/h on dual RAAS blockade (12% reduction in aUkV; $P=0.03$). Mean aUkV at hour 3 was reduced from 3.92 mmol/h on placebo to 3.46 mmol/h on active treatment (12% reduction in aUkV; $P=0.09$). A mixed-effects models approach also demonstrated a statistically significant separation between the placebo and drug curves at hours 2 and 3 ($P=0.03$ hour 2; $P=0.04$ hour 3), consistent with the results of the standard $t$ tests but did not detect a statistically significant delay in reaching maximal potassium excretion, nor significant blunting/flattening of the aUkV versus time curve (Figure 3B). The total amount of potassium excreted during the 5-hour collection did not differ between dual RAAS blockade and placebo ($P=0.14$).

**Fractional Excretion of Potassium**

Dual RAAS blockade was associated with statistically significant reductions in mean FEK (Figure 3C). Mean FEK at hour 2 was reduced from 0.23 on placebo to 0.18 on active treatment (22% reduction; $P=0.005$). Mean FEK at hour 3 was reduced from 0.24 on placebo to 0.19 on active treatment (21% reduction; $P=0.04$).

**Dynamic Changes in Potassium Handling**

Dual RAAS blockade produced statistically significant increases in dynamic K at baseline and at hours 2 and 3 compared with placebo (Figure 3D). Mean dynamic K at hour 2 was increased from 4.72 on placebo to 5.35 on active treatment ($P<0.001$). Mean serum potassium concentration at hour 3 was increased from 4.66 on placebo to 5.32 on active treatment ($P<0.001$).

After the 35-mmol potassium challenge, the modest reduction in potassium excretion with dual RAAS blockade is not of sufficient magnitude to explain the large increase in dynamic K. Dual RAAS blockade was associated with a statistically significant but modest decrease in aUkV from 3.75 to 3.31 mmol/h with no difference in the total amount of potassium excreted during the 5-hour collection period. This observation suggests that the substantial and sustained increase in serum potassium concentration both at baseline and after the 35-mmol challenge produced by dual RAAS blockade was related in large part to impaired extrarenal potassium handling.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Comparison of dynamic potassium handling in participants with CKD vs control participants. A, Mean aUkV rate (mmol/h) vs time. B, Mean FEK vs time. C, Mean dynamic K concentration (mmol/L) vs time. Error bars correspond to ±1 SEM.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Mean ambulatory SEK concentration in participants with CKD treated with lisinopril/spironolactone vs placebo.
Mixed-Effects Models Relating Dynamic Potassium Handling Covariates aUK and Dynamic K to Changes in Ambulatory SEK

We used linear mixed-effects models to predict the relationship between dynamic potassium handling data and drug-induced changes in ambulatory SEK over time. Covariates included changes from baseline with placebo in aUK and dynamic K; MDRD-estimated GFR was included to control for baseline renal function. The fixed-effects estimates for the final model are displayed in Table 2 (see equation; intercept coded at visit 2). Scatter plots of observed versus predicted concentrations and residuals versus predicted concentrations are shown in Figure 4A and 4B.

The change from baseline in dynamic K at hour 3, ΔK, appears to be an important predictor of change in ambulatory SEK induced by dual RAAS blockade. For ΔK equal to zero, the predicted effect of dual RAAS blockade on ambulatory SEK at visit 2 is not statistically significant (\(P=0.84\)). However, nonzero ΔK was found to have a strong influence on this effect: a ΔK of 0.5 mmol/L predicts an approximate 0.235 mmol/L increase in ambulatory SEK (\(P=0.02\)).

This relationship is illustrated in 2 dimensions by a simple plot of the visit-2 drug–placebo ambulatory SEK concentration difference versus the ΔK (Figure 4C [slope=0.63, \(P=0.01\); \(r=0.57\), \(P=0.01\)]).

On the other hand, change from baseline in dynamic aUK, ΔaUK, does not appear to have as quantitatively important an influence on the effect of drug at visit 2 ambulatory SEK (\(P=0.15\)). ΔaUK does have a small inverse effect (\(P=0.03\)) on the slope parameter (indicating the steepness of ambulatory potassium increase). MDRD-estimated GFR has a small inverse influence on visit-2 ambulatory SEK concentration. A decrease of 10 mL/min in MDRD-estimated GFR predicts an

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increase of 0.1 mmol/L in visit-2 ambulatory SEK ($P=0.005$).

Together, the results of our mixed-effects models approach suggests that the change in dynamic $K$ determined at hour 2 after a 35-mmol oral potassium load is a strong predictor of the rise in ambulatory SEK with dual RAAS blockade and appears to be a stronger predictor than the change in $\text{aU}K\text{V}$ in the setting of impaired renal function.

**Discussion**

Dual RAAS blockade has demonstrated beneficial effects in cardiovascular and renal disease but may be associated with hyperkalemia, especially in the common clinical setting of reduced renal function. We sought to investigate the mechanisms of impaired dynamic renal potassium handling with dual RAAS blockade in subjects with renal impairment and to determine whether dynamic renal potassium handling variables can predict changes in ambulatory SEK with dual RAAS blockade.

The first objective of this clinical trial was to compare the mechanisms of dynamic renal potassium handling in study participants with impaired renal function versus control participants with normal GFR. Participants with CKD demonstrated markedly reduced potassium excretion compared with control subjects but were able to maintain serum potassium concentration in the same range as control subjects at baseline and after a 35-mmol challenge, a finding that is consistent with a compensatory increase in extrarenal potassium disposition such as translocation of potassium into the intracellular space or possibly gastrointestinal secretion/malabsorption. In our small group of CKD patients, this was associated with a reduced aldosterone response and a preserved or perhaps even increased insulin response to potassium challenge compared with control participants.

Our observations support those of Perez, who found that potassium translocated into the intracellular compartment estimated by indirect calculations was greater for subjects with renal impairment than for control subjects. Therefore, extrarenal potassium handling appears to be a key compensatory mechanism to maintain a stable SEK response to an oral potassium challenge in the setting of impaired renal potassium excretion.

To investigate the mechanisms of impaired renal potassium handling induced by dual RAAS blockade in participants with CKD, we compared the effects of 4 weeks of dual RAAS blockade versus placebo on dynamic renal potassium handling. We selected 25 mg of spironolactone because this dosage is comparable to dosages used in clinical trials and used in clinical practice. Lisinopril (40 mg) was selected because it represents a high dose of ACE inhibitor consistent with titration in clinical practice. Lisinopril is eliminated by renal clearance and therefore may accumulate in renal impairment. This could lead to variability in response and could produce enhanced ACE inhibitor effects. Nevertheless, lisinopril is a commonly prescribed ACE inhibitor and has been used effectively in patients with renal impairment.

Dual RAAS blockade was associated with a statistically significant but modest decrease in $\text{aU}K\text{V}$, from 3.75 to 3.31 mmol/h, but without a significant difference in the total amount of potassium excreted during the 5-hour collection period. This observation suggests that the substantial and sustained increase in dynamic $K$ both at baseline and after the 35-mmol challenge produced by dual RAAS blockade may be related, in some part to impaired extrarenal potassium handling in addition to reduced potassium excretion. For example, previous work has suggested that aldosterone may be a mediator of the transepithelial distribution of potassium between the extracellular and the intracellular fluid compartments.

Using a mixed-effects models approach, we investigated the quantitative and predictive relationship between the dynamic renal potassium handling variables $\text{aU}K\text{V}$ and dynamic $K$ and ambulatory SEK concentration after institution of dual RAAS blockade. Together, our approach suggests that the change in dynamic potassium handling may be predictive of the rise in ambulatory SEK with dual RAAS blockade. Our mixed-effects models approach offers preliminary support for our hypothesis that acute potassium handling variables (dynamic $K$, $\text{aU}K\text{V}$) may be predictive of changes in ambulatory SEK with dual RAAS blockade.
Perspectives
Our study indicates: (1) renal potassium excretion is markedly blunted in patients with renal impairment who maintain a stable serum potassium concentration by a substantial increase in extrarenal potassium disposition; (2) dual RAAS blockade increases serum potassium concentration at least in part by interfering with extrarenal potassium disposition mechanisms in addition to blunting potassium excretion; and (3) changes in dynamic potassium handling variables are predictive of changes in ambulatory potassium concentration with dual RAAS blockade. Although this latter finding is preliminary and currently has no direct clinical application, such a quantitative relationship could potentially prove useful in developing prediction models to forecast changes in ambulatory SEK concentration with dual RAAS blockade.

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Disclosures
None.

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Mechanisms of impaired potassium handling with dual renin-angiotensin-aldosterone blockade in chronic kidney disease


Division of Clinical Pharmacology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL

Short title: Dual RAAS blockade and potassium handling in CKD
Figure S1. Mean aldosterone concentration (ng/ml) versus time.

Lisinopril/Spironolactone

Placebo

Figure S1. Mean aldosterone concentration (ng/ml) versus time.
Figure S2. Mean insulin concentration (uIU/ml) versus time.

- Lisinopril/Spironolactone
- Placebo

Insulin (uIU/ml) versus Hours post oral potassium load.

Figure S2. Mean insulin concentration (uIU/ml) versus time.