Hyperkalemia, Renal Failure, and Converting-Enzyme Inhibition
An Overrated Connection

Néstor H. García, Sandra T. Baigorria, Luis I. Juncos

Abstract—Hyperkalemia is widely viewed as a common complication of ACE inhibition in azotemic patients. These renal failure patients are the patients who benefit most from ACE inhibition. Because we could not confirm this notion after a retrospective evaluation of 236 azotemic patients, we studied 2 models of renal mass reduction. In the first, we did a 5/6 nephrectomy (Nx) on rats and studied them 2 weeks after surgery (before chronic renal changes had developed). A second group was studied 16 weeks after Nx, once chronic renal failure was established. Rats in both models were treated with quinapril in drinking water. After baseline evaluation, we challenged them either by a high-K⁺ diet or by blocking aldosterone receptors. We found that although quinapril blocked the K⁺-induced increase in aldosterone, serum K⁺ levels and K⁺ balance were maintained before and during high K⁺ intake or during simultaneous spironolactone administration. We conclude that in hemodynamically stable rats with reduced renal mass and renal dysfunction, the administration of an ACE inhibitor does not cause severe hyperkalemia. (Hypertension. 2001;38[part 2]:639-644.)

Key Words: renin-angiotensin system • angiotensin converting-enzyme inhibitors • potassium • nephrectomy

Inhibition of the renin-angiotensin system (RAS) in azotemic patients is viewed as a potential cause of severe hyperkalemia.¹ ² In this respect, isolated reports have shown episodes of life-threatening hyperkalemia.³ In addition, fewer retrospective studies, and even fewer prospective studies, have shown increased serum K⁺ in azotemic patients taking ACE inhibitors (ACEIs).⁴ ⁵ The hyperkalemia is thought to result from aldosterone inhibition secondary to decreased angiotensin (Ang) II production.⁶ However, the final balance is also affected by serum K⁺ and by Na⁺ and water delivery to distal secretory sites.⁷ Still, the prevailing idea is that K⁺ balance in renal failure is preserved by a rise in aldosterone production, whereas urine flow, fecal excretion, and intracellular K⁺ distribution are largely neglected.⁸ According to this notion, ACEI should take away the major component of K⁺ homeostasis in renal failure.⁹

Yet, despite the widespread use of ACEI to curb the progression of renal failure, current evidences fail to show that ACEIs cause clinically severe hyperkalemia. In fact, azotemic patients on ACEIs develop important elevations of serum K⁺, mostly in 2 sorts of settings. In one, the patient receives >1 medication capable of causing hyperkalemia, and thus, there is summation of effects.³ Alternatively, abnormal systemic hemodynamics (as in congestive heart failure) may cause severe renal vasoconstriction and thereby decrease GFR and tubular flow. In these situations, high K⁺ results from combination of multiple factors. These notions suggest that other factors such as urinary flow, fecal excretion, and cellular uptake may contribute to K⁺ balance in renal failure.

Furthermore, low aldosterone levels are short-lived, returning to basal values at variable periods of time.⁹ ¹⁰ This return of aldosterone to values seen in normal subjects suggests that long-term aldosterone synthesis can be regulated by mechanisms other than Ang II. This notion is supported by studies in wild-type (Agt⁺/⁺) and homozygous angiotensinogen deletion mutant (Agt⁻/⁻) mice that show comparable aldosterone levels during normal- and low-sodium diets.¹¹ The expected elevation of aldosterone levels during a low-salt diet is associated with a marked increase in adrenal zona glomerulosa cells and adrenal P450aldo mRNA. Interestingly, Agt⁻/⁻ mice showed a higher plasma K⁺ level than that of Agt⁺/⁺ mice, indicating that a powerful angiotensin-independent mechanism exists for aldosterone secretion and, contrary to current belief, that the tonic effect of high K⁺ on aldosterone synthesis does not require an intact RAS. Thus, these results suggest that K⁺ can be regulated in the absence of aldosterone and that aldosterone synthesis can be regulated independently of Ang II.

Because none of these studies directly address K⁺ balance during impaired renal function when Ang II synthesis is inhibited, we designed this study to determine whether ACEI prevents K⁺ balance in rats with impaired renal function. To address this objective, we first looked retrospectively the records of hypertensive patients with documented renal failure being treated with ACEIs to confirm our impression that clinically significant hyperkalemia does not occur in these patients. Then, we tested the hypothesis that ACEIs do not induce hyperkalemia in a hemodynamically stable condition.
dissected free, and then the entire right kidney and about two thirds of the parenchyma of the left kidney (upper and lower pole included) were excised. Sham groups underwent all anesthetic and surgical procedures except for nephrectomy.

The rats were divided into 3 groups: sham, reduced renal mass (RRM), and chronic renal failure (CRF). The sham and RRM were studied 2 weeks after the 5/6 nephrectomy (Nx). RRM rats, although portraying great nephron loss, have a mild decrease of GFR, hypertrophy of the remnant kidney, and slight fibrosis. In contrast, CRF rats were studied 16 weeks after Nx. The elapsed time in this model allows for more severe renal failure, marked fibrosis, and reduced ability to adapt to a K⁺ load.

**Metabolic Studies**

Rats with normal renal function were divided in a sham A (control group) and a sham B, receiving quinapril (30 mg/L) in drinking water from day 1 to 14. Similarly, both RRM and CRF rats were divided in groups RRM-A and CRF-A (Nx controls), and group B received quinapril in drinking water (30 mg/L) throughout the study (RRM-B and CRF-B). All sham and RRM rats were placed in metabolic cages 2 weeks after Nx. CRF rats were placed in metabolic cages 16 weeks after Nx. For the next 14 days, we measured K⁺ balance in all models. Balances were calculated as the difference between the K⁺ ingested and the K⁺ excreted in feces and urine.

First, we examined the K⁺ handling in ACE-inhibited rats. This was done sequentially on the standard diet (K⁺ 0.5%) for the first 7 days and then on a high-K⁺ diet (3%) from day 8 to 14. In this way, we assessed the response to ACEI in rats with RRM and with CRF on normal- and high-K⁺ diets.

In a second group of rats, we attempted to inhibit any residual aldosterone effect with spironolactone as a challenge instead of the high-K⁺ diet. Groups RRM-C and CRF-C were controls, whereas groups RRM-D and CRF-D received quinapril (30 mg/L) in drinking water throughout the study. From day 8 through day 14, all groups were given spironolactone (15 mg/100 g of food). The mean dose according to food intake was 3 mg/d. In these studies, we attempted to see whether an added inhibitory effect on aldosterone prevented K⁺ homeostasis. Blood was obtained before and after the high-K⁺ diet and before and after administration of spironolactone. Blood pressure, serum K⁺, creatinine clearance, and plasma aldosterone were measured before and after the high-K⁺ diet and spironolactone. Potassium, aldosterone, plasma renin activity, and tail-cuff blood pressure were measured as previously reported.

**Statistical Analysis**

Values shown are mean ± SE. Unpaired and paired 2-tailed t test, and 2-way ANOVA were used when indicated. A P < 0.05 was accepted as a significant change.

## Results

### Sham Controls

In both sham A and sham B rats, serum K⁺ and plasma aldosterone were normal and remained unchanged after the high-K⁺ diet. GFR in sham A and sham B rats was 1.4 ± 0.4 and 1.2 ± 0.1 mL/min, respectively, and remained unchanged by high-K⁺ diet.

### RRM Model

GFR in the RRM-A group was lower than that in sham A rats (0.97 ± 0.04 mL/min) and continued to decrease further after the high-K⁺ diet (P < 0.03) (Figure). In contrast, in RRM B rats (on quinapril), GFR was 1.3 ± 0.2 mL/min, not different from sham B rats, and remained unchanged after the high-K⁺ diet. Under these conditions, serum K⁺ during the standard diet was 3.7 ± 0.1 mmol/L in RRM-A rats and 4.2 ± 0.1 mmol/L in RRM B rats on quinapril (P < 0.01)

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**TABLE 1. Mean Serum K⁺ and Creatinine in Patients on ACEI for Various Lengths of Time**

<table>
<thead>
<tr>
<th>Duration of Treatment</th>
<th>Serum K⁺, mmol/L</th>
<th>Serum Creatinine, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 month (n=28)</td>
<td>4.39±0.1</td>
<td>2.69±0.3</td>
</tr>
<tr>
<td>&lt;12 months (n=79)</td>
<td>4.54±0.1</td>
<td>2.15±0.1</td>
</tr>
<tr>
<td>&gt;12 months (n=101)</td>
<td>4.37±0.1</td>
<td>1.85±0.1</td>
</tr>
<tr>
<td>Controls (n=152)</td>
<td>4.36±0.1</td>
<td>2.72±0.2</td>
</tr>
</tbody>
</table>

For this, we used 2 rat models, one with acutely reduced nephron mass and the other with reduced renal mass but with established chronic renal failure. We realize that none of these models strictly portray most situations of diffuse renal disease, but they served our purpose of assessing potassium homeostasis under conditions of reduced nephron mass, reduced GFR, and ACEI.

**Methods**

The retrospective study was done using records of 236 hypertensive azotemic patients attending 4 Gambro Healthcare Clinics in Argentina. We excluded patients taking furosemide, nonsteroidal antinflammatory drugs, β-blockers, or insulin. The mean age was 60 years (range, 13 to 92 years); the male/female ratio, 0.97; and the mean rectal temperature at 37°C to 38°C. Both adrenal glands were anesthetized with ether and placed on a heated table to maintain homeostasis under conditions of reduced nephron mass, and creatinine, n = 91.6 ± 0.5 mm Hg. Serum K⁺ was 0.8/91.6 (range, 13 to 92 years); the male/female ratio, 0.97; and the mean

**Experimental Models**

Studies were done on male Sprague-Dawley rats weighing 250 to 350 g and maintained on a standard rodent diet (0.5% K⁺). Renal mass reduction was induced as reported. Briefly, the rats were anesthetized with ether and placed on a heated table to maintain rectal temperature at 37°C to 38°C. Both adrenal glands were

**TABLE 2. Serum K⁺ in Patients in Relation to Duration of Treatment and Serum Creatinine**

<table>
<thead>
<tr>
<th>Serum Creatinine, mg/dL</th>
<th>Control</th>
<th>&lt;1 Month</th>
<th>1–72 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.4</td>
<td>4.3±0.1</td>
<td>4.3±0.1</td>
<td>4.6±0.1</td>
</tr>
<tr>
<td>1.4–3</td>
<td>3.9±1.1</td>
<td>4.4±1.1</td>
<td>5.1±3</td>
</tr>
<tr>
<td>&gt;3</td>
<td>4.6±3</td>
<td>4.5±1.1</td>
<td>5.0±1</td>
</tr>
</tbody>
</table>
However, after the high-K\(^+\) diet, serum K\(^+\) in both groups had evened out because of a significant rise in the RRM-A group \((P<0.01)\), whereas RRM-B rats (taking quinapril) showed no changes. The rise in serum K\(^+\) in the RRM-A group was coupled with an increase in aldosterone levels \((P<0.05)\). This was an expected finding because a high-K\(^+\) diet stimulates aldosterone release. In contrast, in group B taking quinapril, plasma aldosterone did not increase during the high-K\(^+\) diet (Table 3). This diminished aldosterone response in rats on quinapril is expected too. The K\(^+\) balance studies showed a slightly more positive balance during the high-K\(^+\) diet in RRM-A rats \((P<0.01)\). This is consistent with the observed rise in serum K\(^+\) and explains the increment in aldosterone. The better K\(^+\) handling in the B group on quinapril could be due to the higher GFR in these animals. Next, we assessed the effects of blocking aldosterone receptors with spironolactone in RRM rats on quinapril. GFR fell in both groups C and D \((P<0.01\) for both) but stayed higher in the RRM-D group (on quinapril) \((P<0.05)\) (Table 3). Only in RRM-D rats, spironolactone caused a rise in serum K\(^+\) \((P<0.01)\). In both groups, plasma aldosterone levels remained unchanged despite the changes in serum K\(^+\). The K\(^+\) balance remained near zero in both groups before spironolactone but, upon adding the drug, became slightly less positive in RRM D rats (on quinapril) compared with RRM C rats \((P<0.01)\). Nevertheless, in both groups the balance remained very close to zero. The rise in serum K\(^+\) (though within normal range), the stable GFR, and the kaliuretic response may have contributed to the steady balance when quinapril accompanied spironolactone. These findings indicate that aldosterone is not critical to maintain K\(^+\) homeostasis in this experimental model.

**CRF Model**

In CRF groups, GFR was lower than that in sham rats (Table 3). During the high-K\(^+\) diet, the mean serum K\(^+\) in CRF-A animals rose 0.3±0.1 mmol/L \((P<0.01)\) but did not change in CRF-B animals (on quinapril). The mild rise in serum K\(^+\) in CRF-A rats after the high-K\(^+\) diet, was followed by a rise in serum aldosterone \((P<0.04)\), whereas in CRF-B rats the aldosterone elevation by high-K\(^+\) diet was blunted. Both CRF groups were in correct K\(^+\) balance while on the standard diet and became positive on starting the high-K\(^+\) diet. Despite marked kaliuresis, CRF-B rats (on quinapril) had a slightly more positive balance during the high-K\(^+\) diet, and yet, serum K\(^+\) remained normal. These findings point to an intact
capacity to readapt to a K⁺ load in rats with CRF even when taking ACEI.

Finally we looked at the combined effects of quinapril and spironolactone in CRF rats. In both groups, CRF-C and CRF-D (quinapril) GFR was lower than that in sham rats and was unchanged by spironolactone. In CRF-C rats, serum K⁺ increased significantly after spironolactone (P<0.05) (Table 3) Similarly, serum K⁺ in the CRF-D rats increased with spironolactone by 0.2 mmol/L (P<0.01). In the CRF-C group, the rise in serum K⁺ was followed by a rise in plasma aldosterone. In contrast, in the CRF-D group on quinapril, the rise in K⁺ was not increased by increased aldosterone levels, as if quinapril was blunting such an effect (P<0.01). Potassium balance was similar in both groups before and after spironolactone. A tendency toward K⁺ retention in both groups was not significant. These results indicate that K⁺ homeostasis in CRF rats is affected very little during aldosterone antagonism.

**Discussion**

This research was prompted by a retrospective study that could not confirm the risk of severe hyperkalemia in patients with CRF on ACEI. Thus, we attempted to reenact 2 clinical settings. In the first one, a major loss of renal mass initiates functional adaptation and compensatory growth, both of which reach a maximal effect at ~2 weeks. At the same time, GFR is maximally restored at ~2 to 4 weeks after Nx. In the second situation, blood pressure increases, inducing progressive fibrosis and major loss of renal function. In models replicating both situations, we first inhibited ACE and then challenged them with a large load of K⁺ or by administering spironolactone. In both models we failed to induce hyperkalemia, not by ACEI, by increasing the dietary K⁺ by a factor of 6, or by combining ACEI to spironolactone. Our findings are in fact supported by published data. Yet, we are often reminded of the risks of ACEI-induced hyperkalemia in azotemic patients.

The fear to hyperkalemia in patients on ACEI, is the first of 2 notions that are frequently accepted without proper evidence. For instance, Ahuja et al reported a 38.6% incidence of hyperkalemia in azotemic patients. However, this retrospective uncontrolled study offers no data on hemodynamic status or additional drugs being taken. Moreover, in many of these patients, serum K⁺ was controlled with simple dietary changes. Keilani et al administered ramipril to 13 patients with overt proteinuria and azotemia. With a 10 mg dose, serum K⁺ rose from 4.53 to 4.78 mmol/L, hardly a clinically significant change. Similarly, Textor et al found no changes in serum K⁺ in azotemic patients taking captopril when the plasma renin activity was low. In azotemic patients with high plasma renin activity and a decrease in aldosterone after captopril, serum K⁺ rose from 3.6±0.1 to 4.4±0.1 mmol/L.

This change, though significant, cannot be called clinically important. Bakris et al comparing lisinopril and an Ang II receptor antagonist, found a increase in serum K⁺ of 0.28 mmol/L above the basal mean of 4.6 mmol/L. Similarly, diabetics with mild renal failure and hyporeninemic hypoaldosteronism, often develop mild to moderate hyperkalemia. Life-threatening situations are usually associated to renal hemodynamic derangements. In summary, most studies in
well-hydrated azotemic patients with stable hemodynamics do not show severe hyperkalemia, but rather harmless elevation.\textsuperscript{18,19}

The second notion standing on little evidence is that blockade of aldosterone synthesis by ACEI is a key mechanism for K\textsuperscript{+} retention. In our study we found that ACEI in rats with RRM and CRF had a blunted aldosterone response when challenged with a high-K\textsuperscript{+} diet. Even though plasma aldosterone did not rise, (probably due to quinapril), hyperkalemia did not occur. These findings suggest that aldosterone is not essential for the maintenance of K\textsuperscript{+} homeostasis in rats with variable degrees of renal failure. Moreover, the addition of spironolactone produced a minor effect too and only in rats with CRF on quinapril (the mean rise in serum K\textsuperscript{+} was 0.2 mmol/L). These findings support the notion that aldosterone is not critical for K\textsuperscript{+} homeostasis and contrasts with the currently held view (based on indirect evidence) that low aldosterone levels cause hyperkalemia in azotemic patients on ACEI. As an example, a correlation between aldosterone and fractional K\textsuperscript{+} excretion in azotemic patients on ACEIs have been taken as evidence of a cause-effect relationship for hyperkalemia.\textsuperscript{20} It seems unlikely though, that decreased aldosterone alone could pose a critical limit to K\textsuperscript{+} secretion if other mechanisms were fully functional. Although aldosterone rises as renal function becomes impaired, other mechanisms may be more important. In fact, fractional excretion of K\textsuperscript{+} in the remnant kidney increases up to 146\%,

\textsuperscript{21} but it is not increased further by large doses of 9α-fluorohydrocortisone or decreased by keeping adrenalectomized dogs with renal failure on fixed doses of deoxy corticosterone. Thus, it seems unlikely that the adaptive rise in K\textsuperscript{+} excretion is regulated by aldosterone. Moreover, K\textsuperscript{+} adaptation seems to require an intact collecting duct, in particular a specific rise in Na\textsuperscript{+}, K\textsuperscript{+}-ATPase activity.\textsuperscript{22} This is unrelated to aldosterone because the rise in Na\textsuperscript{+}, K\textsuperscript{+}-ATPase activity induced by K\textsuperscript{+} occurs in adrenalectomized animals.\textsuperscript{23}

Similarly, sheep on a high K\textsuperscript{+} intake achieve substantial increases in K\textsuperscript{+} excretion unrelated to either aldosterone or serum K\textsuperscript{+}.\textsuperscript{24} Moreover, a high-K\textsuperscript{+} diet increases K\textsuperscript{+} secretion in isolated perfused rabbit CCD even in adrenalectomized animals.\textsuperscript{25} At the single-channel level, aldosterone stimulation by a low-Na\textsuperscript{+} diet or infusion of aldosterone do not increase SK channel density (the channel responsible for K\textsuperscript{+} secretion).\textsuperscript{26} These channels increase during high K\textsuperscript{+} intake.\textsuperscript{26}

Thus, it would appear that the kidney does not rely only on aldosterone but also on other powerful mechanisms, the most salient of which is K\textsuperscript{+} itself. In fact, it would seem that the rate of K\textsuperscript{+} load to the tubule is of the utmost importance. In this respect several tubular mechanism could be playing a role. First, inhibition of Ang II synthesis diminishes proximal sodium and water reabsorption and thereby K\textsuperscript{+} reabsorption. Second, a greater K\textsuperscript{+} intake could increase paracellular K\textsuperscript{+} excretion, and third, a high-K\textsuperscript{+} diet is known to increase K\textsuperscript{+} channels in the collecting duct.\textsuperscript{26} This K\textsuperscript{+}-induced increase in channel density does not result from higher expression of ROMK mRNA but from decreased protein degradation.\textsuperscript{27} At any rate, serum K\textsuperscript{+} levels irrespective of aldosterone\textsuperscript{28} regulate ROMK expression in the renal medulla. Our studies, although not directly addressing these nonaldosterone mech-

anisms of K\textsuperscript{+} adaptation, do show that animals with RRM and CRF adapt to K\textsuperscript{+} loads independently from aldosterone secretion.

A low tubular K\textsuperscript{+} load could result from a low GFR because of effenter arteriole dilatation during ACEI. This may be of concern in clinical states were GFR is critically dependent on Ang II (such as a poststenotic kidney or in severe heart failure or volume depletion). ACEI could cause a reversible decrease in GFR. In fact, most of the reported cases of severe hyperkalemia, azotemia, and ACEIs are plagued with hemodynamic complications. Others are patients receiving K-sparing diuretics, a scenario that promotes volume depletion, diminished GFR and K\textsuperscript{+} retention. Even so, the combination of spironolactone and ACEI is recommended in the treatment of congestive heart failure with or without diminished renal function.\textsuperscript{29,30}

Finally, and because ACEIs are known to improve insulin sensitivity, changes in intra-cellular K\textsuperscript{+} distribution could play a part in keeping serum K\textsuperscript{+} levels within normal range.

In summary, our study shows that animals with reduced renal mass and chronic renal failure treated with ACEI have decreased aldosterone levels. These animals are able to maintain serum K\textsuperscript{+} within normal range even when challenged with a high-K\textsuperscript{+} diet or after the blockade of aldosterone.

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References


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