K⁺ Depletion and the Progression of Hypertensive Disease or Heart Failure

The Pathogenic Role of Diuretic-Induced Aldosterone Secretion

John H. Laragh, Jean E. Sealey

After the introduction of chlorothiazide in 1958,¹ as the first of many sulfonamide thiazide diuretics, these orally active diuretics rapidly became the cornerstone for treatment of patients with congestive heart failure (CHF) and other edematous states. These diuretics were also widely adopted for primary or adjuvant antihypertensive drug therapy. Since the beginning, it was recognized that such natriuretic-diuretic therapy in both of these disorders is regularly accompanied by demonstrable body potassium and magnesium deficiencies, often reflected by significant, albeit generally mild, observed decrements in plasma K⁺ and Mg²⁺ levels. But because no particular problems were recognized with broad use of these diuretics, over the years physicians became increasingly sanguine about their occurrence. Accordingly, thiazide diuretics and then, beginning in 1966, the similar but more powerful loop diuretics (eg, furosemide) also became broadly used as primary or adjuvant treatments for high blood pressure and for the edematous state of CHF, cirrhosis with ascites, and nephrotic syndrome.

Superior Features of Spironolactone Over Sulfonamide Diuretics for Treating Hypertension or CHF

The first selective aldosterone receptor antagonist, spironolactone (Aldactone), was introduced in clinical medicine in 1958.² By blocking the action of aldosterone, it proved to be a potent natriuretic-diuretic and K⁺-retaining agent. Thus, it produced diuresis and weight loss with no loss of K⁺ or Mg²⁺, something our group views as a great conceptual therapeutic advantage over thiazides. The lack of any demonstrable morbidity from thiazide-induced K⁺ depletion and the impressive prompt diuresis that these drugs produced at a low cost, however, carried the sulfonamide diuretics into a leadership position for treatment of hypertension or edematous states that continues today.

Our preference for the aldosterone antagonist approach, however, was enhanced by 2 facts. First, in outpatient trials, in >20 reports of head-to-head comparisons of spironolactone with a thiazide diuretic, spironolactone proved to be at least as effective as the thiazides for correcting hypertension²;

and second, spironolactone treatment proved to be considerably more potent than thiazides and/or furosemide for full diuresis of patients with CHF or cirrhosis with ascites, often working after a failed thiazide/Lasix trial. Its power in these latter 2 situations was therefore amazing. Furthermore, these latter results correctly implied a large role for aldosterone excess in the pathogenesis of these conditions.

In addition to cost, however, there are 2 problems with spironolactone that have stalled its acceptance: First is its very gradual action, which made it appear to be less effective and therefore less attractive to anxious physicians and patients. It takes 3 to 5 weeks of daily therapy to express its full effect. This is because spironolactone blocks only that 2% of the daily renal sodium resorption that is governed by aldosterone. At this rate, however, cumulative sodium loss becomes large, so that after 4 weeks or so, it may easily exceed what could be achieved over the same time with a loop diuretic. This scenario is similar to what happens after total adrenalectomy in animals. These animals die of salt loss and/or hyperkalemia (the model counterpart of an Addisonian crisis), but this takes 6 weeks to develop, and the process can of course be delayed or avoided by feeding NaCl. The second problem with spironolactone was that it caused unpleasant dose-related antiandrogenic side effects, especially in the dose of 50 to 100 mg/d used at first. These are gynecomastia in men and menstrual disturbances in women. But as time went on, we learned that this could be largely avoided by giving only 12.5 to 25 mg/d.

With this latter information in hand, one of us (J.H.L.) over the years achieved success after success as a consultant for treating desperate cardiac patients, already receiving full doses of Lasix and an ACE inhibitor, by adding a small daily dose of spironolactone and then observing, time and time again, dramatic natriuresis and diuresis without urinary K⁺ loss but with clearing of all edema fluid plus an obvious improvement in total cardiovascular performance that sometimes added years to the lives of these patients.

The RALES Heart Failure Trial

We shared these experiences and views about spironolactone with Dr John Alexander, with whom we had worked on

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TABLE 1. Changes in Serum and Skeletal Muscle K⁺ During Diuretic Therapy in Patients With CHF and Hypertension

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<tr>
<td></td>
<td>Normal</td>
<td>EHT on Diuretic</td>
</tr>
<tr>
<td>Serum K⁺, mmol/L</td>
<td>4.05</td>
<td>3.55 (−12%)</td>
</tr>
<tr>
<td>Tissue K⁺, mmol/100 g fat-free dry solids</td>
<td>43.8</td>
<td>40.4 (−8%)</td>
</tr>
<tr>
<td>Intracellular K⁺, mmol/kg intracellular water</td>
<td>130</td>
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EHT indicates essential hypertension.

Muscle K⁺ Depletion: A Common Pathogenic Factor in Thiazide-Treated CHF and Hypertensive Patients

The spectacular results of the RALES trial in CHF patients taught us that sulfonamide-diuretic-induced K⁺ and Mg²⁺ deficiencies may not be benign. This per se could create serious dysfunction in cardiac and skeletal muscle performances, which, in CHF, might hasten progression of heart failure. This possibility is strongly supported by the large measured deficiencies in muscle K⁺ and Mg²⁺ with increased muscle Na⁺ content in muscle biopsies of either diuretic-treated CHF or diuretic-treated hypertensive patients in studies reported by Dyckner et al.¹⁻⁶ (Table 1). They also demonstrated impressive corrections of those muscle disturbances by superimposed spironolactone therapy, which blocks the kaliuretic and magnesiumuretic actions of endogenous aldosterone. These results teach us anew that the K⁺ (and Mg²⁺) loss in these patients is caused or amplified by the diuretic-induced high plasma renin and angiotensin, and thence plasma aldosterone, levels occurring in CHF, which are also induced in hypertensive patients by their similar renin-aldosterone system response to the thiazide-induced sodium-volume loss.⁷⁻⁹ Accordingly, this kidney renin secretary response in either CHF or hypertension can be turned off by restoring NaCl to improve volume and flow, after which renin and aldosterone fall dramatically, but this treatment may restore hypertension, and it is not safe to apply in most CHF patients.⁷

Thus, in CHF, heart failure begins in the heart with its failure as a pump,¹⁰ leading to poor renal perfusion that causes the kidneys to release renin, causing plasma renin-angiotensin to rise, which in turn stimulates aldosterone release, which causes Na⁺ retention (and edema), but if aldosterone is high and if distal tubular sodium supply is also too high, as occurs with diuretic therapy,¹¹ kaliuresis will be sustained. Thus, in this setting of chronic diuretic therapy, the volume depletion of thiazide or loop diuretics causes renin and especially, thence, aldosterone¹¹,¹² to increase, causing aldosterone to maintain chronic kaliuresis. All of this is correctable by spironolactone blockade of the aldosterone receptor. Long ago, Davis¹⁰ demonstrated the crucial role of aldosterone in dog heart failure. This heart failure was dramatically corrected by total adrenalectomy, and then it could be restored by aldosterone replacement.¹⁰ Spironolactone does the same job in patients, albeit much less dramatically or completely than would a surgical adrenalectomy.

Pathogenic Role of Thiazide-Induced K⁺ Depletion in Hypertensive Patients

Great clinical discoveries, like this one from the RALES Trial,³ revealing a discrete pathogenic role for thiazide-induced increased distal tubular sodium supply enabling the endogenous aldosterone excess to sustain kaliuresis¹¹ and thereby facilitating the progression of CHF via depletion of myocardial and vascular K⁺, are often first made in the most egregious forms of a disease. Accordingly, by extrapolating from these findings in CHF, one can recognize the very same long-term thiazide-induced biochemical pathophysiology (ie, high aldosterone and low K⁺ levels) as it occurs, not only in milder forms of heart failure but also in that vast population of diuretic-treated hypertensive patients who are available. Thus, practically all thiazide-treated hypertensive patients do exhibit lower plasma K⁺ levels than before their thiazide therapy.

Hypokalemia With Diuretic Use in the SHEPS Trial

The recent subgroup analysis of the Systolic Hypertension in the Elderly (SHEPS) trial¹³ is directly relevant to the latter issue. A subgroup of this study, which used low-dose chlorthalidone, revealed that 7.2% of the treated hypertensive patients exhibited plasma K⁺ values <3.5.³ Surprisingly, in these diuretic-treated hypokalemic patients, all of the potential protection from morbid cardiovascular sequelae was lost.¹³ This loss of cardioprotection occurred even though...
their blood pressures remained reduced below even the control group (Table 1). These findings resemble earlier findings in the MRFIT trial of a 2.4-fold greater risk of sudden death associated with higher-dose diuretic therapy.14,15 Moreover, these relationships are entirely in keeping with earlier studies by Cannon and colleagues8,9 that showed that urinary K\textsuperscript{+} loss in diuretic-treated patients, who have either hypertension or heart failure, is consistently closely related to the height of endogenous aldosterone secretion rates (Figure 1). They also showed that the kaliuresis of diuretic therapy does not occur in adrenalectomized patients, thereby proving that it is the aldosterone response to diuretic-induced sodium-volume depletion, not the diuretic itself, that causes the kaliuresis.9 Moreover, we have learned that higher renin and aldosterone levels in response to diuretic treatment can also reverse its antihypertensive effect.12

K\textsuperscript{+} Depletion Impairs Cardiac Performance

We know that body K\textsuperscript{+} depletion can occur without subnormally reduced plasma K\textsuperscript{+} levels, so that what we are seeing in hypokalemic patients could be a tip of the iceberg situation. In this regard, thiazide diuretic treatment of hypertensives is associated with more ventricular arrhythmias16,17 and higher sudden death rates,18 and these events are avoided by spironolactone.18 The converse of these relationships is also true. In a human trial23 and in our study of stroke-prone hypertensive animals,24 high K\textsuperscript{+} diets were associated with stroke protection in humans. In the SHRsp rats, K\textsuperscript{+} repletion was associated with impressive reductions in their renin levels and with arrest of vascular pathology in the heart, brain, and kidneys, along with the stroke protection (see Figures 2 and 3).

Two studies by Young and associates illustrate how mild potassium depletion produces impressive impairment of cardiac function in normal dogs and healthy human volunteers. In the dog study, mild K\textsuperscript{+} depletion reduced the maximal rate of filling in response to volume expansion by 51%, and in the human study, a mean K\textsuperscript{+} value of 3.5 reduced peak flow velocity measured by echocardiography by 14%.20

K\textsuperscript{+} Depletion Is a Sine Qua Non for Full Expression of Experimental Hypertensive Vascular Damage to Heart, Brain, and Kidney Vessels in Various Hypertensive Models

In rat genetic hypertension (SHRsp rats), diuretic or dietary K\textsuperscript{+} depletion appears to be a prerequisite for the occurrence of subsequent heart, brain, and kidney vessel cardiac injury, all of which are accordingly corrected or arrested by increasing the dietary K\textsuperscript{+} intake or, even better, by treatment with spironolactone.21,22 The converse of these relationships is also true. In a human trial23 and in our study of stroke-prone hypertensive animals, high K\textsuperscript{+} diets were associated with stroke protection in humans. In the SHRsp rats, K\textsuperscript{+} repletion was associated with impressive reductions in their renin levels and with arrest of vascular pathology in the heart, brain, and kidneys, along with the stroke protection (see Figures 2 and 3).

### Table 2. Number and Rates of Cardiovascular Events According to Hypokalemia After 1 Year

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<tr>
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<th>Active Treatment</th>
<th>Placebo</th>
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<tr>
<td>K\textsuperscript{+} &gt; 3.5</td>
<td>27.9 (n=1951)</td>
<td>50 (n=151)</td>
</tr>
<tr>
<td>K\textsuperscript{+} &lt; 3.5</td>
<td>143±18</td>
<td>140±13</td>
</tr>
<tr>
<td>Cardiovascular event rate per 1000 person-years</td>
<td>27.9</td>
<td>50</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>143±18</td>
<td>140±13</td>
</tr>
</tbody>
</table>

induced reductions in blood pressure. Moreover, increasing dietary K⁺ without also blocking endogenously high aldosterone levels probably has little corrective value in diuretic-treated patients,23 because unless aldosterone is also blocked, the fed K⁺ is directed into the urine by the endogenous aldosterone excess8,9 induced in both CHF and hypertensive patients by thiazide diuretic activation of the renin system8,9 and by the thiazide action to divert more sodium to the distal nephron. Accordingly, short of stopping the thiazide therapy, the value of specific aldosterone receptor antagonists, such as spironolactone, for treating such patients with hypertension or heart failure appears to be unique for dealing with this iatrogenic predicament. Spironolactone treatment per se, that is, as a replacement for thiazide therapy, could well prove to be an even simpler solution. Newer analogues with possibly even fewer endocrine side effects will be welcome.

Several biochemical or cellular mechanisms have been implicated to explain how K⁺ depletion promotes cardiac and vascular injury, which is correctable by K⁺ repletion. Thus, increases in extracellular K⁺ levels within the physiological range in 1-mmol/L, increments from 3 to 7 mmol/L causes significant decreases in free radical formation from vascular endothelial cells, smooth muscle proliferation, and induced thrombus formation.24 With verification, these pathways could prove to be relevant clinical targets for pharmacological control.

In summary, thiazide-induced K⁺ and/or Mg²⁺ depletion in hypertension and in CHF is probably not benign. It impairs cardiac function, and it creates or enhances the risk of morbidity and vascular events. In hypertensive patients, these effects of K⁺ depletion more than cancel the cardiovascular protective value afforded by the concurrent sizable thiazide-

**References**


**Key Words:** potassium ■ hypertension ■ heart failure ■ aldosterone ■ spironolactone
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