Review

The Cardiovascular Implications of Hypokalemia

Steven G. Coca, DO, Mark A. Perazella, MD, and Gregory K. Buller, MD

The role of potassium in the progression of cardiovascular disease is complex and controversial. Animal and human data suggest that increases in dietary potassium, decreases in urinary potassium loss, or increases in serum potassium levels through other mechanisms have benefits in several disease states. These include the treatment of hypertension, stroke prevention, arrhythmia prevention, and treatment of congestive heart failure. Recently, the discovery that aldosterone antagonists not only decrease sodium reabsorption and decrease potassium secretion in the nephron, but also decrease pathological injury of such nonepithelial tissues as the myocardium and endothelium, has generated great controversy regarding the actual mechanisms of benefit of these agents. We review the available data and draw conclusions about the relative benefits of modulating potassium balance versus nonrenal effects of aldosterone blockade in patients with cardiovascular disease. Am J Kidney Dis 45:233-247. © 2004 by the National Kidney Foundation, Inc.

INDEX WORDS: Potassium; hypertension; arrhythmia; myocardial infarction (MI); congestive heart failure (CHF); aldosterone.

IN TYPICAL MODELS of cardiovascular disease progression, sodium is the major cation that garners most attention. Clearly, the role of sodium in directly modulating extracellular volume and contributing to systemic hypertension and congestive heart failure (CHF) is important. However, potassium may be an equally important factor in modifying the progression of cardiovascular disease.

The human body contains approximately 3,500 mEq (mmol) of potassium, of which 98% is contained in the intracellular space. Extracellular potassium concentration is regulated tightly between 3.5 mEq/L (mmol/L) and 5.0 mEq/L (mmol/L). However, various dietary, hormonal, and pharmacological stressors influence potassium homeostasis. These disturbances in potassium homeostasis may have important cardiovascular implications.

Hypertension

Pathophysiological Characteristics

Animal and human studies show an intimate inverse relationship between potassium level and blood pressure (BP). Various vasculoprotective properties of potassium have been elucidated. First, potassium decreases BP by several mechanisms (Table 1). Potassium supplementation results in natriuresis1,2 by decreasing proximal tubular reabsorption of sodium,3 directly inhibiting renin release,4,5 and increasing glomerular filtration rate.

From the Section of Nephrology, Yale University School of Medicine, New Haven; and Department of Internal Medicine, St Mary's Hospital, Waterbury, CT.

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Address reprint requests to Steven G. Coca, DO, Fellow in Nephrology, Yale University School of Medicine, FMP 107, PO Box 208029, 333 Cedar St, New Haven, CT 06520-8029. E-mail: steven.coca@yale.edu

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through a reduction in renal vascular resistance.\textsuperscript{6} Potassium also may function directly as a vasodilator by stimulation of $\text{Na}^{+}/\text{H}^{+}, \text{K}^{+}/\text{H}^{+}$-adenosine triphosphatases, resulting in hyperpolarization and smooth muscle relaxation\textsuperscript{7}; by decreasing vascular reponsiveness to angiotensin II\textsuperscript{8}; and by increasing nitric oxide production.\textsuperscript{1} Second, increases in potassium levels inhibit oxygen free radical formation from vascular endothelial cells and macrophages,\textsuperscript{9} proliferation of vascular smooth muscle cells,\textsuperscript{10} and platelet aggregation and arterial thrombosis.\textsuperscript{11} High-potassium diets appear to protect the endothelium from hypertension-induced dysfunction\textsuperscript{12} and reduce macrophage adherence to the vascular wall.\textsuperscript{13} All these effects act to limit vascular injury and normalize BP.

\textit{Animal Data}

Experimental studies suggest that potassium supplementation decreases BP in animals. Diets rich in potassium have been shown to decrease BP in stroke-prone spontaneously hypertensive rats (SHRSPs)\textsuperscript{14-16} and Dahl salt-sensitive (DS) rats.\textsuperscript{1,16} Increased potassium intake also has been shown to abrogate cerebral vascular lesions and reduce mortality independent of the BP reduction. In SHRSPs fed a 4\% sodium chloride diet for 17 weeks, potassium supplementation reduced mortality from 83\% to 2\% ($P < 2 \times 10^{-6}$).\textsuperscript{16} Comparison of SHRSPs with the highest BPs in the potassium-supplemented (addition of 1.36\% potassium) group with SHRSPs with the lowest BPs in the non–potassium-supplemented group showed that mortality was reduced by 86\% (from 64\% to 9\%; $P < 0.003$) in the potassium-supplemented group despite identical mean BP (212 mm Hg) measurements in the 2 groups.\textsuperscript{16} In DS rats, potassium supplementation reduced overall mortality from 55\% to 4\% ($P < 10^{-6}$). Again, in a group of DS rats with matched BPs (205 mm Hg), the potassium-supplemented group experienced an 87\% reduction in mortality, from 38\% to 5\% ($P < 0.001$).\textsuperscript{16} Additional study of the long-term effects of potassium supplementation in SHRSPs during a 5-month period showed a 91\% reduction in mortality ($P < 10^{-6}$), largely on the basis of a marked reduction in intracerebral hemorrhage.\textsuperscript{16} This study was replicated by the same researchers the following year, with virtually identical results.\textsuperscript{17}

Additional studies confirmed the BP-independent vasculoprotective properties of potassium supplementation in SHRSPs with a high sodium intake.\textsuperscript{18} High potassium intake for 12 weeks was shown to attenuate the increases in plasma renin activity and BP, significantly reducing the incidence of stroke and overall mortality to rates similar to those following the control diet despite equal BPs (Table 2).

High potassium intake also has been shown to significantly reduce the degree of nephrosclerosis in SHR\textsuperscript{19} and DS\textsuperscript{20} rats independent of changes in BP. In DS rats fed 4\% sodium chloride diets, the addition of potassium citrate or

<table>
<thead>
<tr>
<th>Table 1. Vasculoprotective Properties of Potassium</th>
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<tbody>
<tr>
<td>Decreases blood pressure</td>
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<tr>
<td>Natriuresis</td>
</tr>
<tr>
<td>Decreases proximal sodium reabsorption</td>
</tr>
<tr>
<td>Decreases renin release</td>
</tr>
<tr>
<td>Increases glomerular filtration rate</td>
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<tr>
<td>Vasodilator</td>
</tr>
<tr>
<td>Stimulates $\text{Na}^{+}$, $\text{K}^{+}$-adenosine triphosphatases</td>
</tr>
<tr>
<td>Decreases responsiveness to angiotensin II</td>
</tr>
<tr>
<td>Increases nitric oxide production</td>
</tr>
<tr>
<td>Decreases oxygen free radical formation</td>
</tr>
<tr>
<td>Decreases proliferation of vascular smooth muscle cells</td>
</tr>
<tr>
<td>Decreases platelet aggregation and arterial thrombosis</td>
</tr>
<tr>
<td>Decreases hypertension-induced endothelial dysfunction</td>
</tr>
<tr>
<td>Decreases macrophage adherence to vascular wall</td>
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</tbody>
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<thead>
<tr>
<th>Table 2. Differences in Plasma Renin Activity and Rates of Stroke, Renal Lesions, and Death After 12 Weeks of Intake of a Regular, High Sodium Chloride, or High Sodium Chloride/High Potassium Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity</td>
</tr>
<tr>
<td>Stroke (%)</td>
</tr>
<tr>
<td>Renal vascular damage (%)</td>
</tr>
<tr>
<td>Death (%)</td>
</tr>
<tr>
<td>Regular</td>
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<tr>
<td>High Sodium Chloride/High Potassium</td>
</tr>
<tr>
<td>High Sodium Chloride</td>
</tr>
<tr>
<td>7.8</td>
</tr>
<tr>
<td>11.1</td>
</tr>
<tr>
<td>25.3*</td>
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<tr>
<td>7.7</td>
</tr>
<tr>
<td>24.5</td>
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<tr>
<td>81.1*</td>
</tr>
<tr>
<td>7.9</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>79††</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>25.3</td>
</tr>
<tr>
<td>50.5‡‡</td>
</tr>
</tbody>
</table>

NOTE. Regular diet includes 0.35\% sodium chloride, 1.1\% potassium chloride; high sodium/high potassium diet, 4\% sodium chloride, 2.11\% potassium citrate; high sodium chloride diet, 4\% sodium chloride, 0.75\% potassium chloride.

* $P < 0.0001$ versus both other groups.
† $P < 0.05$ versus high sodium chloride/high potassium group.
‡ $P < 0.01$ versus regular diet group.
§ $P < 0.05$ versus both other groups.

Data from Volpe et al.\textsuperscript{18}
potassium chloride prevented 30% to 50% of tubular lesions and 20% of glomerular lesions. Furthermore, potassium supplementation reduced renal artery wall thickness, increased arterial lumen size, and prevented decreases in renal papillary blood flow. There were no significant differences in BPs between the potassium-supplemented and non–potassium-supplemented groups.

Aldosterone is a mineralocorticoid that acts on epithelial cells, specifically, principal cells in the cortical collecting duct, to stimulate sodium reabsorption and potassium secretion. Additionally, aldosterone recently was discovered to have activity on nonepithelial tissues, specifically, the endothelium and myocardium. Recently, a group of studies by Rocha et al examined the pathogenic role of aldosterone in vascular disease and the benefits of its blockade. SHRSPs infused with aldosterone developed severe proteinuria and renal vascular damage. Whereas subsequent treatment with captopril reduced plasma aldosterone levels and prevented the development of proteinuria and renal vascular and glomerular lesions, aldosterone infusion completely restored renal lesion development and proteinuria in these captopril-treated SHRSPs without changing BP, supporting a toxic effect of aldosterone.

In another study, treatment of SHRSPs with spironolactone reduced proteinuria from protein of 150 mg/d to 39 mg/d (P < 0.0001), reduced the cerebrovascular lesion score (P < 0.1), reduced renal vascular and glomerular lesions (P < 0.001), and prolonged survival (P < 0.03). Finally, angiotensin II infusions were able to reverse the renal protection afforded by captopril in SHRSPs. However, in these captopril-treated SHRSPs infused with angiotensin II, the selective aldosterone antagonist eplerenone was able to reduce proteinuria (protein, 96 versus 28 mg/d; P < 0.0001) and glomerular (16% versus 4%; P < 0.001) and renal vascular lesions (17% versus 4%; P < 0.001), with no significant difference in BP between groups.

Conversely, 2 studies do not necessarily support a specific role for aldosterone blockade in the prevention of vascular injury. Green et al found that treatment with spironolactone for 4 weeks was not able to reduce glomerular sclerosis or proteinuria in the remnant kidney model. Another study found that treatment of SHRSPs drinking a 1% sodium chloride solution with amiloride, an epithelial sodium channel blocker with great specificity for the epithelial sodium channel in the cortical collecting duct (ENaC) and no antimineralocorticoid activity, reduced proteinuria (protein, 119 versus 15 mg/d; P < 0.002) and markedly prolonged survival. Six of 8 SHRSPs treated with amiloride survived past 20 weeks of age, whereas all control SHRSPs died of stroke by 16.4 weeks (P < 0.0001). There were no significant differences in BP with treatment with amiloride and no significant differences were detected in urinary potassium excretion, creating ambiguity about how amiloride afforded benefit in this study.

In summary, several studies provide evidence for the vascular protective roles of potassium supplementation, aldosterone antagonism, and ENaC blockade. However, it is uncertain how much of the benefit of aldosterone antagonists or amiloride is confounded by their ability to decrease urinary potassium losses, increase serum potassium levels, and increase sodium excretion. To date, no direct comparison studies of potassium supplementation versus either pharmacological modality on hypertension, stroke, and renal injury have been performed in animals.

Epidemiological Characteristics

It is important to know whether animal data translate into clinical effects. One can assess this in part through epidemiological examination of dietary potassium effects in humans. Dietary potassium intake in the United States varies greatly, ranging from very low intake, particularly in African Americans, of approximately 25 mEq (mmol) per day to approximately 200 to 250 mEq (mmol) per day in those who consume large amounts of fruits and vegetables. Diets deficient in potassium may be an important pathogenic factor in arterial hypertension and hypertension-related morbidity and mortality, especially in African Americans. Potassium depletion has been shown to exacerbate hypertension, even when patients are placed on sodium-restricted diets. In large epidemiological studies, dietary potassium intake has correlated inversely with both systolic and diastolic BP. These data suggest that serum potassium concentrations independently influence BP.
**Clinical Trials**

Potassium supplementation has been shown to decrease BP in multiple clinical trials, as well as in 2 meta-analyses. Whelton et al reviewed results of 33 randomized clinical trials and found that potassium supplementation reduced systolic BP by 3.11/1.97 mm Hg overall and by 4.4/2.5 mm Hg in hypertensive patients. In 81% of studies analyzed in this meta-analysis, potassium supplementation was associated with a trend toward reduction in systolic BP, and in 34% of the trials, systolic BP reduction was statistically significant. African Americans benefited most, with BP reductions nearly 3 times greater than those in Caucasians. Additionally, BP reductions were greater in those with greater levels of urinary sodium excretion, greater initial BPs, and those treated for a longer period with potassium supplementation.

Furthermore, 2 studies suggested that potassium may have important BP-independent vascular protective properties. The first, a 12-year prospective population study, showed that increases in dietary potassium (10 mEq/d [mmol/d]) reduced the risk for stroke mortality by 40% (P < 0.001), and this effect was greater than one would expect from the BP reduction achieved alone. The second study investigated the association between dietary habits and stroke in 43,738 men. In this study, a 38% relative risk reduction (P = 0.007) for stroke was found in men with potassium intake in the highest quintile compared with the lowest quintile, even after adjustment for changes in BP.

**Animal Data**

Animal models repeatedly have shown a great frequency of ventricular tachycardia/ventricular fibrillation (VT/VF) with the induction of hypokalemia, especially in the setting of acute myocardial infarction (MI). Furthermore, the rates of VT/VF are reduced when normal potassium concentrations are restored.

**Epidemiological Characteristics of Arrhythmias in Acute MI**

The strongest epidemiological evidence that hypokalemia increases risk for ventricular arrhythmias has been shown repeatedly in the setting of acute MI (Table 3). Although the risk for VT/VF correlates with infarct size, there is a greater independent risk for VT/VF with increasing severity of hypokalemia. The greatest risk for hypokalemia-associated VT/VF is within the first few hours of presentation. Hypokalemia occurs in this situation for 2 reasons: (1) high circulating catecholamine levels during acute MI, resulting in a β2-dependent shift of potassium into cells; and (2) frequent treatment with diuretics before hospitalization. The coalescence of myocardial damage (serving as an irritable electrical focus), high catecholamine levels, and hypokalemia no doubt serve to magnify the risk for ventricular arrhythmia and make it difficult to separate out the primary effects of hypokalemia. One might postulate that a larger myocardial infarct results in greater catecholamine release and therefore more pronounced hypokalemia. However, studies have not found a relationship between infarct size and hypokalemia, possibly because catecholamine-induced hypokalemia is ameliorated by the release of intracellular potassium from the ischemic myocardium.

**Clinical Trials Related to Arrhythmias in Acute MI**

No clinical trials have examined the potential benefits of aggressive potassium repletion for the reduction of ventricular arrhythmias in the setting of acute MI. However, given the strong relationship between hypokalemia and ventricular arrhythmias in patients with acute MI, it is prudent to aggressively replete potassium in patients with acute MI to levels greater than 4.0 mEq/L (mmol/L), as typically is done in clinical practice.
It is plausible to hypothesize that the beneficial effects of nonselective $\beta$-blockers in the setting of acute MI are related in part to changes in serum potassium levels. Nonselective $\beta$-blockade may be superior to selective $\beta_1$-blockade in preventing ventricular arrhythmias. This effect likely stems from the reduction in the $\beta_2$-associated shift of potassium into cells and associated hypokalemia. Treatment with the nonselective $\beta$-blocker timolol increased serum potassium concentration by 0.41 mEq/L (mmol/L) at 2 hours after MI and by 0.92 mEq/L (mmol/L) at 4 hours after MI and reduced the incidence of hypokalemia by approximately 50%.56 Data for ventricular arrhythmias were not reported in this trial. In a larger study of 735 patients examining the use of a nonselective $\beta$-blocker in patients with acute MI, propranolol reduced the incidence of VF from 3.7% to 0.5% compared with placebo ($P = 0.006$).57 Furthermore, Johansson and Dziamski55 found that nonselective $\beta$-blockade reduced the incidence of ventricular arrhythmias in hypokalemic patients with acute MI, whereas selective $\beta$-blockade did not.55

**Epidemiological Characteristics of Arrhythmias in Hypertension**

Treatment of patients with hypertension with thiazide diuretics frequently promotes hypokalemia. This occurs through increases in distal sodium delivery in the nephron and by activation of the renin-angiotensin-aldosterone system (RAAS). Controversial for several years, it has been unclear whether this metabolic derangement of potassium homeostasis was clinically important, not only by interfering with BP-lowering effects, but also by inducing ventricular arrhythmias and sudden death. Because the frequency of sudden cardiac death in hypertensive patients is relatively infrequent, it has been difficult to draw meaningful conclusions from the available studies. For instance, in the Multiple Risk Factor Intervention Trial, there were 36 coronary heart disease deaths in the special-intervention treatment group and only 21 deaths in the usual-care control group.58 The risk for coronary heart disease death, mostly from sudden cardiac death, was increased 3-fold by diuretic treatment in patients with abnormal baseline resting electrocardiograms. The incidence of hypokalemia was 3 times greater in the special-intervention group compared with the usual-care group, suggesting an association of diuretic-induced hypokalemia and coronary heart disease death. It also is interesting to note that sudden cardiac death rates were not decreased in several randomized studies that used diuretics despite a significant

**Table 3. Studies Examining Risk for VT/VF in the Setting of Acute MI in Relation to Serum Potassium Level**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Association</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulting49</td>
<td>1,315</td>
<td>Yes</td>
<td>Potassium $&lt;3.9$ mEq/L associated with 5-fold increase in VT*</td>
</tr>
<tr>
<td>Solomon and Cole50</td>
<td>151</td>
<td>Yes</td>
<td>VT/VF in 48% of patients with potassium $&lt;3.5$ mEq/L v 21% with potassium $&gt;3.5$ mEq/L</td>
</tr>
<tr>
<td>Nordrehaug51</td>
<td>1,035</td>
<td>Yes</td>
<td>VF in 16% of patients with potassium $&lt;3.5$ mEq/L v 7% with potassium $&gt;3.5$ mEq/L†</td>
</tr>
<tr>
<td>Nordrehaug et al52</td>
<td>60</td>
<td>Yes</td>
<td>Probability of VT 0.68 with potassium $&lt;3.5$ mEq/L v 0.10-0.22 with potassium $&gt;4.0$ mEq/L</td>
</tr>
<tr>
<td>Nordrehaug and Von der Lippe53</td>
<td>1,074</td>
<td>Yes</td>
<td>VF in 17.2% of patients with potassium $&lt;3.5$ mEq/L v 7.5% with potassium $&gt;3.5$ mEq/L†</td>
</tr>
<tr>
<td>Dyckner et al64</td>
<td>676</td>
<td>Yes</td>
<td>VT/VF in 40% of patients with potassium $&lt;4.3$ mEq/L v 27% with potassium $&gt;4.3$ mEq/L†</td>
</tr>
<tr>
<td>Johansson et al65</td>
<td>5,877</td>
<td>Yes</td>
<td>Incidence of VF increased by 2.0- to 2.5-fold when potassium $&lt;3.5$ mEq/L‡</td>
</tr>
</tbody>
</table>

**NOTE.** To convert potassium in mEq/L to mmol/L, multiply by 1.

* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.
reduction in BP with these agents.\textsuperscript{59-63} The reduction in BP in hypertensive patients would be expected to decrease the rate of sudden cardiac death.

Two case-control studies suggested that diuretic-related hypokalemia may be associated with sudden death.\textsuperscript{64,65} Sisocvick et al\textsuperscript{64} found a dose-dependent relationship between thiazide use and sudden death. Interestingly, no risk reduction was noted to be associated with concurrent potassium chloride supplementation. After adjustment for other risk factors, thiazide plus potassium-sparing diuretics reduced the risk for primary cardiac arrest by 70\% relative to thiazides alone. Hoes et al\textsuperscript{65} similarly found that patients administered a thiazide diuretic alone had an increased risk for sudden death (odds ratio, 1.8) compared with a reference group treated with a thiazide plus a potassium-sparing diuretic.

\textit{Clinical Trials Related to Arrhythmias in Hypertension}

In the Systolic Hypertension in the Elderly Program trial, patients with isolated systolic hypertension were randomly assigned to a thiazide-based antihypertensive regimen versus placebo. The treatment group experienced a significant reduction in major cardiovascular events associated with the BP reduction afforded by the thiazide.\textsuperscript{66} However, subsequent analysis showed that no morbidity or mortality benefit was noted for the 7.2\% of participants with a serum potassium level less than 3.5 mEq/L (mmol/L) after 1 year of active treatment with chlorthalidone.\textsuperscript{67} This represented a greater than 50\% increase in risk for major cardiovascular events in the actively treated patients who experienced hypokalemia compared with those who had normal serum potassium levels.\textsuperscript{67} Importantly, the apparent ineffectiveness of therapy was not caused by interference of the antihypertensive effects of chlorthalidone because systolic BP was lower in hypokalemic patients (140 mm Hg) compared with those who were eukalemic (143 mm Hg). The exact cause for the loss of cardiovascular protection is not completely clear, but one can speculate an increased risk for stroke, ventricular arrhythmia, or endothelial dysfunction as the potential reason. This result is hypothesis generating and may have been an artifact of subgroup analysis.

Finally, the Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial, the largest single prospective study to date involving the treatment of hypertension, did not support the hypothesis that thiazide-type diuretics increase the risk for sudden death.\textsuperscript{68} In the study, 42,418 patients were randomly assigned to administration of chlorthalidone, amlodipine, lisinopril, or doxazosin. Although patients in the diuretic group had significantly lower serum potassium levels at 2 and 4 years of follow-up compared with patients administered the other drugs, there was no increase in mortality. However, to date, no analysis of the hypokalemic subgroup similar to that in the Systolic Hypertension in the Elderly Program study has been performed. Regardless, given the large number of patients and the randomized controlled nature of the trial, these data may be the most convincing evidence that hypokalemia may not be an important factor for the development of sudden cardiac death in the treatment of straightforward hypertensive patients.

\textit{Arrhythmias in the Hemodialysis Population}

During hemodialysis, serum potassium concentration is rapidly decreased as patients are dialyzed against a 2.0-mEq/L (mmol/L) potassium bath (rarely, 1.0 mEq/L [mmol/L]). This rapid reduction in serum potassium level is not without consequence, and the incidence of ventricular arrhythmias is increased during hemodialysis, ranging from 9\% to 40\% in some reports.\textsuperscript{69-73} In 400 patients who experienced cardiac arrest, 17\% were prescribed a 0- or 1-mEq/L (mmol/L) potassium bath compared with 9\% of control patients.\textsuperscript{74} Serum potassium level is lowest during the last hour of hemodialysis, and the incidence of arrhythmias is greatest in the last hour of dialysis and persists for as long as 5 hours after dialysis.\textsuperscript{71,72} Additional support for this association is shown in hemodialysis patients who experience a greater decrease in intraerythrocytic potassium concentration because they are more prone to the development of arrhythmias.\textsuperscript{76} Finally, QT dispersion, an important predictor of ventricular arrhythmias, increases during hemodialysis.\textsuperscript{77} A decrease in serum potassium level during hemodialysis is associated with an increase in QT dispersion.\textsuperscript{78} Importantly, com-
pared with isokalemic dialysate, a 2.0-mEq/L (-mmol/L) potassium bath nearly doubled the number of patients who developed an increase in QT dispersion.78

CONGESTIVE HEART FAILURE
Pathophysiological Characteristics
The presence of hypokalemia in the milieu of CHF has 3 important consequences: (1) impaired diuresis because of decreased natriuresis,4,5 (2) impaired myocardial performance,80,81 and (3) increased risk for ventricular arrhythmia and sudden death82-86 (Table 4). Hypokalemia and total-body potassium depletion in patients with CHF is common for several reasons: First, frequent use of diuretics to control fluid overload results in kaliuresis.87,88 Second, the RAAS is activated through decreased effective circulating volume from ventricular dysfunction89-91 and results in additional kaliuresis.92,93 Third, the presence of high levels of circulating catecholamines94 may rapidly decrease serum potassium concentration through β2-receptor activation and shift of potassium into cells.95,96 Fourth, metabolic alkalosis resulting from diuretic use stimulates the intracellular shift of extracellular potassium and promotes renal excretion of potassium (Table 5).97

Experimental Data
Hypokalemia can affect both cardiac structure and function. In experimental animals, potassium deficiency leads to myocardial necrosis and fibrosis98-100 and can be prevented by potassium supplementation.99,101 Severe potassium deficiency also is associated with widespread myocardial fibrosis in humans.102 Furthermore, myocardial contractile and relaxation responses are decreased in patients with hypokalemia.81,103 In response to epinephrine, hypokalemic dogs have a lower inotropic response, lower peak rate of change of ejection power, and lower maximal rate of decrease in left ventricular (LV) pressure.103 In response to volume expansion, hypokalemic dogs have a lower maximal stroke volume index and maximal cardiac index.103 In healthy human volunteers, hypokalemia similarly impairs diastolic relaxation to a clinically significant degree, evidenced by higher isovolumetric relaxation times and deceleration time of flow through the mitral valve.84

There also are considerable data implicating aldosterone as a negative-effector hormone in patients with CHF. It appears to cause adverse effects by inducing myocardial and vascular fibrosis,104-113 myocardial necrosis,114,115 endothelial dysfunction,116 and impaired baroreceptor responsiveness.117 In cell-culture studies, incubating cardiac fibroblasts with aldosterone results in increased collagen production, which is abolished by the addition of spironolactone.118 Supporting the hypothesis that aldosterone has adverse effects ultimately affecting the myocardium, mineralocorticoid receptor antagonism111-115 or adrenalectomy114,115 attenuated LV hypertrophy (LVH),111,112,114,115 reduced myocardial necrosis,114,115 and reduced myocardial fibrosis111,112 in rats with renovascular hypertension111-113 or rats infused with angiotensin II,115 angiotensin II/Nο-nitro-L-arginine methyl ester (an inhibitor of nitric oxide synthase),114 or aldosterone.111-113 Controversy exists about whether aldosterone is acting through changes in sodium and potassium balance with subsequent changes in BP or whether these effects are through direct actions through mineralocorticoid receptors on the myocardium.

Table 4. Consequences of Potassium Depletion in Patients With CHF

| Impaired diuresis |
| Impaired myocardial performance |
| Increased risk for arrhythmia |
| Increased risk for mortality from sudden death and progressive cardiac failure |

Table 5. Causes of Hypokalemia in Patients With CHF

| Diuretics |
| Activate the RAAS |
| Increase sodium delivery to distal nephron |
| Metabolic alkalosis |
| LV dysfunction |
| Activation of the RAAS |
| Activation of the adrenergic system |
| High circulating catecholamine levels |
| Increase intracellular shift of potassium (β2 receptor) |
| Activate the RAAS |
sis\textsuperscript{114,115} and myocardial fibrosis\textsuperscript{111-113} were accomplished independent of reductions in BP, leading the investigators to conclude that it was direct effects on the myocardium. However, mineralocorticoid antagonism, as expected, led to significant changes in serum or urinary sodium and potassium levels in most studies,\textsuperscript{111-113,115} whereas in others,\textsuperscript{114} these values were not reported (Table 6). Some investigators alluded to this potential confounding variable in their conclusions.\textsuperscript{111,115}

Five studies have tried to directly elucidate this mechanism. Young et al\textsuperscript{110} attempted to confirm that aldosterone directly caused these adverse effects on the myocardium, rather than hypertension or hypokalemia. In this study, potassium supplementation (0.4% potassium chloride) in uninephrectomized rats fed 1% sodium chloride diets infused with aldosterone did not reduce the development of interstitial or perivascular fibrosis. Rats kept normotensive through intracerebral infusion with the mineralocorticoid receptor antagonist RU-28318 and administered exogenous aldosterone developed LVH and fibrosis.\textsuperscript{110} The investigators concluded that myocardial fibrosis occurs independently of hypokalemia, hypertension, and cardiac hypertrophy. Whereas this and other studies have shown that cardiac fibrosis can occur independently of hyper-
tension and cardiac hypertrophy,\textsuperscript{108,111,112} we believe this study severely handicapped the potential effect of potassium homeostasis on myocardial fibrosis because only 0.4% potassium chloride was added to the drinking solution and serum potassium levels remained in the hypokalemic (<3.5 mEq/L [mmol/L]) range in the supplemented groups. This amount of supplementation is markedly less than that in studies of potassium supplementation published by Tobian et al.\textsuperscript{20}

The second study is the only study that directly compared the effects of mineralocorticoid antagonism with potassium supplementation.\textsuperscript{119} Here, Wistar rats administered N\textsubscript{ω}-nitro-L-arginine methyl ester and angiotensin II along with 1% sodium chloride for 14 days developed biventricular myocardial injury. The extent of myocardial damage was reduced by consumption of a low-sodium diet (\(P < 0.05\)) or eplerenone (\(P < 0.001\)), but the addition of 1.1% potassium chloride to the diet had no effect.\textsuperscript{119} Differences in BP did not account for any of the results. However, it is not clear in this study whether sufficient elevation in serum potassium levels occurred because this was not reported. Plasma aldosterone levels were reported, which decreased from 30 ng/dL (0.83 nmol/L) in the control group to 21 ng/dL (0.58 nmol/L) in the potassium-supplemented group.\textsuperscript{119} This is unex-

### Table 6. Studies Suggesting Benefit on Myocardial Fibrosis by Aldosterone Antagonists in Animals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Baseline Conditions</th>
<th>Treatment</th>
<th>Length of Treatment (wk)</th>
<th>Outcome</th>
<th>Confounders</th>
<th>Sodium/Potassium Balance Modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>Aldosterone, 0.75 (\mu\text{g}/\text{h}), or RHT</td>
<td>Spironolactone</td>
<td>8</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>112</td>
<td>Aldosterone, 0.75 (\mu\text{g}/\text{h}), or RHT</td>
<td>Low- and high-dose spironolactone</td>
<td>8</td>
<td>Yes</td>
<td>Yes</td>
<td>Decreased</td>
</tr>
<tr>
<td>113</td>
<td>Aldosterone, 0.75 (\mu\text{g}/\text{h}), or RHT</td>
<td>Spironolactone</td>
<td>8</td>
<td>No</td>
<td>Yes</td>
<td>Mild decrease</td>
</tr>
<tr>
<td>114</td>
<td>L-NAME, ATII, sodium chloride</td>
<td>Eplerenone</td>
<td>2</td>
<td>NA</td>
<td>Yes</td>
<td>No change</td>
</tr>
<tr>
<td>115</td>
<td>ATII, sodium chloride</td>
<td>Eplerenone</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>No change</td>
</tr>
<tr>
<td>119</td>
<td>L-NAME/ATII/sodium chloride</td>
<td>Eplerenone (v) low sodium (v) 2.1% potassium chloride</td>
<td>2</td>
<td>Decreased myocardial damage</td>
<td>No change</td>
<td>Serum potassium increased</td>
</tr>
</tbody>
</table>

Abbreviations: RHT, renovascular hypertension; ATII, angiotensin II; L-NAME, N\textsubscript{ω}-nitro-L-arginine methyl ester; MF, myocardial fibrosis.
pected because very small increases in serum potassium levels should stimulate aldosterone release, not suppress it.

Finally, 3 more animal studies further cloud the direct role of aldosterone on the myocardium. Campbell et al.\textsuperscript{120} found that 8 weeks of amiloride therapy prevented the development of myocardial necrosis and reparative fibrosis (fibrosis in response to cellular injury), but not reactive fibrosis (fibrosis in the absence of myocardial injury) in uninephrectomized Sprague-Dawley rats administered 1% sodium chloride and aldosterone infusions at 0.75 \( \mu \text{g/h}. \)\textsuperscript{120} BP was significantly lower, as was urinary potassium excretion. In the second study, uninephrectomized Wistar rats were fed 1% sodium chloride and administered deoxycorticosterone acetate for 4 weeks, producing hypertension, hypokalemia, myocardial scarring, and fibrosis with subsequent diastolic stiffness.\textsuperscript{121} Subsequent treatment with amiloride, 1 mg/kg/d, for 2 weeks completely normalized myocardial scarring, collagen content, and LV compliance. The third study examined 16 transgenic mice showing pseudohypoaldosteronism type 1 phenotype by replacement of the mouse \( \alpha \) subunit of ENaC with rat \( \alpha \)-ENaC subunit under the control of the heterologous cytomegalovirus promoter.\textsuperscript{122} These mice showed sodium wasting, normal BP, and severe hyperaldosteronism to levels 6-fold greater than control. After 16 months with this phenotype, there was no evidence of cardiac hypertrophy, remodeling, or fibrosis in these mice (serum potassium level was not reported). These studies would argue against the hypothesis that myocardial fibrosis is completely aldosterone dependent and instead caused by a composite effect of potassium, sodium, BP, and aldosterone. The relative importance of each factor is still undetermined.

**Epidemiological Characteristics**

Clinically, hypokalemia is an independent risk factor for both ventricular arrhythmias and death in patients with CHF.\textsuperscript{82,83} Two intriguing studies support the deleterious effects of potassium depletion in patients with CHF by modes of increased arrhythmogenesis and impairment of myocardial function. These retrospective analyses of the Studies of Left Ventricular Dysfunction database, including 6,797 symptomatic and asymptomatic patients with an ejection fraction (EF) less than 0.36 randomized to placebo or enalapril treatment, indicate the adverse effect of hypokalemia in patients with CHF. The first analysis showed that treatment with non-potassium-sparing diuretics increased the risk for arrhythmic death by 85\% (\( P = 0.0001 \)).\textsuperscript{123} The second analysis noted a 25\% risk reduction (\( P = 0.03 \)) for death or hospitalization from progressive heart failure in patients administered potassium-sparing diuretics compared with those administered non-potassium-sparing diuretics.\textsuperscript{124} A statistically significant difference in serum potassium levels was noted for the 2 analyzed groups. Neither report specified which potassium-sparing diuretics were used, and the role of potassium supplementation was not examined. If spironolactone was the predominant potassium-sparing diuretic used, it would be difficult to determine whether the benefits of treatment were caused by differences in serum potassium levels or from benefits of aldosterone blockade on nonepithelial tissues.

**Clinical Trials**

Based on the potential pathogenic role of aldosterone and the benefits of aldosterone antagonism in animal models, 2 large randomized controlled trials using aldosterone antagonists in patients with CHF were designed. The Randomized Aldactone Evaluation Study (RALES) randomly assigned 1,663 patients with New York Heart Association class III or IV heart failure and EF less than 35\% to therapy with spironolactone or placebo. A 30\% relative reduction in all-cause mortality was achieved, with statistically significant reductions in sudden cardiac death and death from progressive heart failure.\textsuperscript{125} The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) randomly assigned 6,632 patients who had experienced an acute MI and had an EF less than 35\% to therapy with spironolactone or placebo. A 30\% relative reduction in all-cause mortality was achieved, with statistically significant reductions in sudden cardiac death and death from progressive heart failure.\textsuperscript{125} The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) randomly assigned 6,632 patients who had experienced an acute MI and had an EF less than 40\% and symptoms of CHF or diabetes to eplerenone or placebo treatment. Treatment with eplerenone reduced overall mortality by 15\% (\( P = 0.008 \)), which was driven primarily by a 21\% reduction in sudden cardiac death.\textsuperscript{126}

Based on some of the experimental data discussed, there is great enthusiasm in review articles that the relative risk reduction in mortality witnessed in both studies was caused primarily by the direct effects of aldosterone blockade on cardiac and vascular tissues.\textsuperscript{127-129} However, in
the RALES trial, serum potassium levels were 0.3 mEq/L (mmol/L) greater ($P < 0.001$) in the spironolactone group compared with the placebo group.125 Similarly, in the EPHESUS trial, the incidence of serious hypokalemia (potassium $< 3.5$ mEq/L [mmol/L]) was significantly greater in the placebo group compared with the eplerenone group (13.1% versus 8.4%; $P < 0.001$).126 This reduction in hypokalemia may have decreased hypokalemic-induced VT/VF and sudden death.130 In support of this hypothesis, subgroup analysis showed no mortality benefit for patients who had a baseline serum potassium level greater than 4 mEq/L (mmol/L). Thus, it is possible that increases in serum (and presumably total-body) potassium levels were responsible for the improved clinical outcomes noted in the treatment groups in RALES and EPHESUS. Additionally, the increase in serum potassium levels associated with aldosterone antagonism may represent enhanced urinary sodium excretion and improved volume status. This hypothesis is supported by the RALES dose-ranging study that closely observed the effect of increasing doses of spironolactone on several measures of volume status and electrolyte balance.131 In this study, composed of 214 patients with class II through IV heart failure administered angiotensin-converting enzyme (ACE) inhibitors and loop diuretics, the addition of spironolactone for 12 weeks at doses starting as low as 12.5 mg/d and up through 75 mg/d resulted in statistically significant differences in BP, serum potassium levels, plasma renin activity, and atrial natriuretic factor levels in a dose-dependent manner. The majority of these variables (with the exception of serum potassium level, which was significantly greater with therapy) were not reported in RALES.

There are more human data that question the importance of aldosterone on LV structure, collagen content, and cardiac systolic and diastolic function. Two studies using echocardiography compared differences in cardiac structure and function in patients with primary aldosteronism or essential hypertension.132,133 Despite statistically significant differences in plasma or urinary aldosterone values between the 2 groups, neither study was able to show differences in LV dimensions, wall thickness, mass,132,133 or multiple parameters of systolic132,133 or diastolic132 function between patients with primary aldosteronism or essential hypertension. Instead, multiple regression analysis showed that BP was the most important determinant of LV mass index, and LV mass index correlated with indices of diastolic dysfunction.132

These data are supported by 2 large, double-blind, prospective, controlled trials containing 1,105 and 844 patients followed up for 1 and 4 years in hypertensive patients with LVH, respectively.134,135 In these studies, thiazide diuretics were shown to be equivalent134 or superior135 to ACE inhibitors in reducing LV mass. However, these data contrast with results of 2 meta-analyses.136,137 The first analysis, by Dahlöf et al,136 examined 109 studies from 1977 to 1990. Only 1 study group consisted of more than 38 participants (average, 21 patients) and more than 50% of studies were less than 6 months long. In the second analysis by Klingbeil et al,137 the average number of patients in each study group was 25, and mean study duration was 34 weeks. Finally, a prospective double-blind study that compared hydrochlorothiazide with ramipril138 treatment noted that the thiazide was inferior to the ACE inhibitor in reducing LV mass. However, each study arm contained only 25 participants and was only 6 months long.

These data suggest that angiotensin II and aldosterone may not have as pivotal a role in causing or maintaining LVH in hypertensive patients. However, data from a substudy139 of 261 patients from the RALES support results generated from studies of experimental animals that implicated aldosterone as a mediator of cardiac fibrosis in patients with CHF. High baseline levels of serum markers of cardiac fibrosis were associated with high mortality and hospitalization rates in these patients. The addition of spironolactone decreased levels of these markers of fibrosis, whereas placebo was associated with increased levels. The morbidity and mortality benefit with spironolactone was most prominent in subgroups of patients with the greatest levels of markers of cardiac fibrosis. Also, the Eplerenone, Enalapril, and Eplerenone/Enalapril Combination Therapy in Patients With Left Ventricular Hypertrophy study found that combination therapy reduced LV mass significantly more than eplerenone alone ($-27.2$ versus $-14.5$ g; $P = 0.007$), although BP was significantly lower...
in this group ($P < 0.05$). Again, data that aldosterone blockade reduces cardiac remodeling are incontrovertible. The debate that continues based on conflicting studies published to date is whether these effects are a direct result of aldosterone action on nonepithelial tissues or through changes in potassium and sodium balance and BP. Currently, there are no clinical trials that examine the role of potassium supplementation in modulating outcomes in patients with CHF.

Finally, it should be noted that a recent report indicates that rates of hospitalization for hyperkalemia among patients hospitalized for heart failure who were administered ACE inhibitors increased significantly from 2.4/1,000 patients in 1994 to 11.0/1,000 patients in 2001 ($P < 0.001$) after publication of RALES. In addition, hyperkalemia-associated mortality increased from 0.3 deaths/1,000 patients to 2.0 deaths/1,000 patients ($P < 0.001$). Therefore, caution must be taken in prescribing mineralocorticoid antagonists to patients with CHF. Adherence to the inclusion criteria of RALES and EPHESUS should be practiced, and serum potassium levels and renal function should be monitored frequently to avoid these potentially deadly complications.

CONCLUSION

The exact role of hypokalemia in the progression of cardiovascular disease is complex and mysterious. There appears to be a consistent inverse relationship between potassium intake and BP, particularly in African Americans; mild reductions in BP can be achieved with dietary potassium supplementation. Several animal studies support the vascular protective properties of potassium, aldosterone antagonists, and ENaC blockers. Clinically, increases in potassium intake reduce stroke, likely through BP-dependent and BP-independent mechanisms. No clinical data are available for aldosterone antagonists and ENaC blockers in regard to stroke prevention.

The role of hypokalemia and cardiac arrhythmias is complex. The Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial results argue that aggressive potassium repletion is not essential in the treatment of patients with uncomplicated hypertension with diuretics, dispelling some earlier concerns raised by case-control studies. However, hypokalemia is arrhythmogenic, especially in the setting of acute MI, high catecholamine levels, and/or a hypertrophied or dilated left ventricle. In regard to acute MI, correction of hypokalemia is imperative. Except for the treatment of pulmonary edema, use of non-potassium-sparing diuretics should be limited in the peri-MI period to avoid additional potassium depletion. Based on the current literature, it is not clear whether nonselective $\beta$-blockade is superior to selective $\beta$-blockade.

Finally, in regard to patients with CHF, hypokalemia is an important independent risk factor for morbidity and mortality. Correction of serum potassium levels to between 4.0 mEq/L (mmol/L) and 5.0 mEq/L (mmol/L) seems prudent. In patients who have serum potassium levels less than 4.0 mmol/L, several strategies may be beneficial. Dietary potassium consumption can be increased, ACE inhibitors or angiotensin II receptor blockers, which should already be a part of the regimen for treatment of patients with CHF, should be maximized. Excessive doses of loop and thiazide diuretics should be avoided. Doses should be titrated to maintain stable weight in patients and reduce the development of pulmonary edema. Finally, in patients with a low EF after MI or chronic class III and IV heart failure, aldosterone blockade appears to be the most efficacious therapy through effects to increase serum potassium levels, increase urinary sodium losses, and antagonize deleterious effects of aldosterone on the myocardium and endothelium. At this time, which of these effects of aldosterone blockade confers a greater benefit cannot be determined. Careful monitoring of patients on aldosterone antagonists is imperative to avoid hypokalemia.

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