Hemodynamic Effects of Alterations in Potassium

MARK S. PALLER, M.D., AND STUART L. LINAS, M.D.

SUMMARY Potassium is the major intracellular cation. Despite this fact, the systemic and renal hemodynamic effects of alterations in either serum K or in total body K are only partially understood. In isolated preparations acute K excess causes vasodilation while acute K deficiency results in vasoconstriction. Although chronic K excess may decrease arterial pressure in experimental models of hypertension, no definitive conclusions can be stated on the effect of K excess in hypertensive patients. In normotensive animals, chronic K depletion is associated with decreased systemic vascular resistance and increased renal vascular resistance. Although a number of studies have shown that K depletion ameliorates experimental hypertension, no definitive conclusions can be stated on the effect of K depletion in hypertensive patients. The vasodilatory effect of K depletion appears to be a direct effect on vascular smooth muscle since it is associated with an increase in total body Na as well as an increase in cardiac output and in renin and arginine vasopressin levels. Although renin levels are increased in K deficient rats to a value comparable to Na-depleted rats, angiotensin antagonism results in a substantially smaller decrease in arterial pressure than in Na-depleted rats (11 ± 1.6 vs 24 ± 3.4 mm Hg, p < 0.01). This relative resistance to the pressor effect of angiotensin also results in a blunted pressor sensitivity to exogenous angiotensin II. Since changes in K balance appear to have a major effect on the control of hemodynamics, further studies are warranted to determine whether alterations in K balance would be useful in the treatment of hypertension.

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KEY WORDS • experimental hypertension • renin-angiotensin • vasoconstriction • vasodilation

POTASSIUM is the major constituent cation of all cells. In view of this fact, it is striking that there have been so few studies on the hemodynamic effects of perturbations in total body K. In this brief review, we will outline the current information on this topic and consider several questions: 1) What are the hemodynamic consequences of both K excess and of K deficiency? 2) Are there differences between acute changes in K concentration and chronic changes in K balance? 3) What mechanisms are involved in these hemodynamic effects of K? In particular, are there accompanying changes in Na balance and in the activity of endogenous pressor hormone systems or are the hemodynamic changes a direct result of K on the vascular smooth muscle cell?

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in either sodium (Na) balance or in pressor hormone activity. In studies of isolated perfused limbs by Chen et al., K-induced vasodilation was prevented or reversed when ouabain, an inhibitor of Na-K-ATPase, was added. These investigators postulated that the vasodilator action of K was the result of stimulation of membrane Na-K-ATPase activity, which resulted in membrane hyperpolarization and relaxation of vascular smooth muscle.

**Potassium Excess — Chronic**

In 1928 Addison reported that the administration of K could lower blood pressure (BP) in humans. Moreover, he postulated that the reason for the high incidence of hypertension in the United States was related to the North American diet, which tended to be higher in Na and lower in K than in other parts of the world where hypertension was substantially less prevalent. Since this description, other investigators have also postulated that the relatively low K content of the North American diet may be a cause of hypertension.8-15

There are a number of animal studies that have demonstrated that the administration of very large quantities of K could substantially blunt the hypertensive effect of an extremely high Na diet.8-10 In 1972, Dahl and his associates performed a very interesting study demonstrating that even small increases in K intake resulted in a decrease in blood pressure in hypertension-prone rats fed a high Na diet (fig. 1). In this study rats were fed a 4.5% NaCl diet with varying concentrations of KCl. As the K content of the diet was increased from a diet of normal K content (Na/K ratio of 10) to a diet of high K content (Na/K ratio of 1), systolic BP fell remarkably in these animals despite the high Na intake. Moreover, even smaller increases in dietary K (Na/K ratio of 2 or 3) caused a lowering of systolic blood pressure.

There have been animal studies demonstrating the protective effect of K on other experimental forms of hypertension. For example, Suzuki et al. studied the effect of adding 0.5% KCl to the drinking water of rats with two-kidney, one clip hypertension. Whereas systolic pressure reached a level of 180—200 mm Hg in water-drinking rats, systolic pressure was only 140—150 mm Hg in K-drinking animals. In association with amelioration of hypertension, there was a marked increase in urinary Na and water excretion. In addition, the increase in PRA which is characteristic of two-kidney, one clip hypertension. Whereas systemic pressure reached a level of 180—200 mm Hg in water-drinking rats, systolic pressure was only 140—150 mm Hg in K-drinking animals. In association with amelioration of hypertension, there was a marked increase in urinary Na and water excretion. In addition, the increase in PRA which is characteristic of two-kidney, one clip hypertensive rats was partially attenuated in K-loaded rats. Although the authors postulated that the hypotensive effect of K administration was due to the decrease in PRA and the marked natriuresis and diuresis observed in K-loaded rats, it is also possible that the effect was due to a direct vasodilatory effect of K.

The mechanism of the hypotensive effect of K administration in hypertensive rats is not clear. For example, it has not been determined whether the decrease in blood pressure is caused by a decrease in cardiac output or in systemic vascular resistance. Moreover, it is not known whether the hypotensive effect is due to K administration per se or to the changes in Na balance or in pressor hormone activity that accompany the administration of K. In this regard, the administration of KCl results in a negative external Na balance. Young et al. have studied both normal dogs and adrenalectomized dogs maintained on fixed quantities of both gluco- and mineralocorticoids. When K intake was increased from 30 to 200 mM per day, both groups of animals went into negative Na balance and had a reduction in 22Na space after 6 days of the high K diet. Moreover, adrenalectomized dogs became hypotensive because of greater Na loss and contraction of extracellular fluid volume most likely due to the inability to increase aldosterone secretion. A similar effect of K-loading on Na balance has also been demonstrated in adrenalectomized humans.13 In addition to altering Na balance, the administration of K results in a decrease in activity of renin and angiotensin II but an increase in aldosterone in both experimental animals and humans.14 In summary, the hypotensive effect of K may be multifactorial but at the present time it has never been dissociated from the natriuretic effect of K administration.

There have also been studies exploring the role of K excess in the treatment of hypertensive humans. Probably the studies most often mentioned are those of Kempner employing the rice-fruit diet as the sole therapy of hypertension. Whereas the low Na content
of the diet is well-recognized, its normal-to-increased K content is frequently overlooked as a possible cause of the hypotensive effect of the diet. Several British studies have reexplored the effect of dietary K supplementation in the treatment of hypertension. In one of these studies, subjects were maintained on their usual Na intake or on a diet that was mildly Na restricted and was supplemented with 100 mM of KCl per day. There was no effect of K administration on the blood pressure of normotensive individuals. In contrast, K supplementation initially lowered blood pressure in hypertensive subjects (-8.9 ± 11.2/−6.4 ± 9.4 mm Hg, p < 0.05). However, this effect was not sustained, and by 12 weeks the blood pressure of hypertensive subjects was not significantly different from their baseline. Moreover, since the study period included a diet restricted in Na as well as enriched in K, it is not possible to determine whether the changes in pressure were caused by an excess of K or a decrease in Na.

In summary, whereas the hypotensive effect of K administration has been clearly demonstrated in hypertensive rats, it has not been conclusively demonstrated in hypertensive humans. Further investigation is clearly warranted.

Potassium Deficiency — Acute

Many studies have demonstrated that perfusing isolated vessels, limbs, and organs from normokalemic animals with hypokalemic solutions results in vasoconstriction. For example, when Anderson et al. decreased the K concentration of the blood perfusing the gracilis muscle of the dog by placing a dialyzer on the arterial side of the muscle, vascular resistance increased by 10% when K concentration fell by 40%. The mechanism of the local vasoconstrictor effect of acute hypokalemia is independent of both changes in Na balance and in pressor hormone activity since it can be demonstrated in isolated perfused arterial preparations. It is likely to be a direct effect of vascular smooth muscle, but the precise biochemical events accompanying hypokalemia remain to be defined.

Potassium Deficiency — Chronic

Chronic sustained dietary K deficiency has been demonstrated to result in a decrease in systemic vascular resistance in all but one study in which systemic hemodynamics have been determined. For example, Galvez et al. produced K deficiency in dogs over several weeks and then measured hemodynamic parameters in conscious restrained animals. There was a 33% decrease in vascular resistance. Mean arterial pressure remained unchanged as cardiac output increased to the same extent that vascular resistance fell. Of further interest was the observation that the vasodilatory effect of K occurred despite an increase in total body Na and an increase in plasma volume of 40%.

In the rat, Freed and Friedman originally demonstrated that K deficiency resulted in hypotension. We have also studied the effects of K deficiency on systemic hemodynamics in the rat. For these studies, K was withheld from the diet. Control rats were fed an identical diet to which K had been added. Aside from K, the sodium, calcium, magnesium, chloride, and phosphorous contents of the two diets were comparable. Animals were studied after 14–17 days of K restriction at which time the plasma K was 2.3 mEq/liter compared to 4.1 mEq/liter in control rats. Muscle and kidney K content was decreased by about 18%. Hemodynamic studies were performed by the microsphere methodology in conscious restrained animals.

Table 1 demonstrates the effect of K deficiency on systemic and renal hemodynamics. There was a slight decrease in mean arterial pressure. Just as in the K-deplete dog, systemic vascular resistance was decreased by about 30% while cardiac index was increased but, in contrast to the dog, not quite enough to maintain arterial pressure. Moreover, as previously shown by Sealey et al., balance studies demonstrated the rats to be in positive Na balance, and this increase in total body Na was reflected by an increase in plasma volume (4.08 ± 0.2 vs 3.5 ± 0.1 ml/100 g body weight, p < 0.05). In summary, therefore, despite an increase in total body Na and in plasma volume, chronic dietary K deficiency results in a decrease in systemic vascular resistance and, in the rat, mean arterial pressure.

What about the effects of K deficiency in hypertension? As already noted, Addison and others have suggested that one possible cause of the higher incidence of hypertension in the United States is that the North American diet tends to be low in K. There are, however, a few studies in both man and animals that suggest that K deficiency may actually lower

<table>
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<tr>
<th>Table 1. Effect of K Depletion on Systemic and Renal Hemodynamics in the Conscious Rat</th>
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<tr>
<td>Rat group</td>
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<tr>
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<tr>
<td>K replete</td>
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<tr>
<td>(n = 12)</td>
</tr>
<tr>
<td>K deplete</td>
</tr>
<tr>
<td>(n = 8)</td>
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<tr>
<td>p value</td>
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RBF = renal blood flow; RVR = renal vascular resistance; MAP = mean arterial pressure; CI = cardiac index; and SVR = systemic vascular resistance.
blood pressure in hypertension. Perera studied the effect of dietary K deficiency in five patients with essential hypertension. In this study patients were limited to 25-30 mEq K per day. All five patients had a hypotensive response to K deficiency. The mean decrease in blood pressure was 15/9 mm Hg, and the blood pressure returned to baseline soon after the K-deficient diet was discontinued.

There are two animal studies evaluating the effects of K deficiency on renal hypertension. Rosenman et al. studied rats with one-kidney, one figure-8 hypertension. Animals were placed on a diet of normal K content (0.3%) or on one of two K-deficient diets: 0.03% or 0.006% K. As seen in figure 2, when K was removed from the diet of rats with established hypertension, systolic blood pressure decreased after a 4-week delay. Fisher and Funke have demonstrated a protective effect of K deficiency in rats with two-kidney, one clip hypertension. In these studies, animals were clipped after 6 weeks of a K-deficient diet. Hypertension did not develop in animals maintained on the K-deficient diet. In contrast, animals became hypertensive within 1 week of initiation of a normal K diet.

In preliminary studies, we too have found that K deficiency markedly alters the natural history of two-kidney, one clip renovascular hypertension. Following placement of a 0.25 mm silver clip on the left renal artery, rats were placed on a normal K diet (n = 9) or a K-deficient diet (n = 16). In rats maintained on the normal K diet, systolic blood pressure increased to 133 ± 5 mm Hg (mean ± SEM) 7 days after clipping and reached a value of 149 ± 4 mm Hg by 21 days. In contrast, in K-deficient rats systolic blood pressure only reached a level of 112 ± 4 mm Hg (p < 0.001) after this 3-week period.

In summary, chronic dietary K deficiency results in vasodilation. Further studies are warranted to determine the hemodynamic effects of chronic K deficiency in experimental models of hypertension. Moreover, it is important to recognize that all of these studies have been performed in animals that were at least 15% K-depleted. This corresponds approximately to a 500 mEq deficit in humans, i.e., moderate-to-severe K deficiency.

In addition to altering systemic hemodynamics, dietary K deficiency results in profound changes in renal hemodynamics. In the presence of this remarkable systemic vasodilation, renal vascular resistance was increased and renal blood flow decreased by about 40% in K-deplete rats (table 1). We have recently completed studies on the mechanism of the increase in renal vascular resistance. Since angiotensin levels are increased in the K-deficient rat, the role of angiotensin as a renal vasoconstrictor was determined. The administration of either saralasin or teprotide lead to a substantial increase in renal blood flow in K deficient animals (fig. 3). However, since renal blood flow remained less than in control rats, it appeared that there was a second renal vasoconstrictor present. In recently published studies, Beck et al. have demonstrated that thromboxane production is increased in kidneys from K-deficient rats. Since thromboxane is a vasoconstric-
tor product of prostaglandin metabolism, the role of thromboxane as a vasoconstrictor in K deficiency was determined by utilizing prostaglandin cyclooxygenase inhibitors and a selective thromboxane synthetase inhibitor. Figure 3 demonstrates that cyclooxygenase inhibition with meclofenamic acid resulted in a substantial increase in renal blood flow in K deficient animals. Identical results were obtained utilizing indomethacin and the selective thromboxane synthetase inhibitor, indomethacin. Moreover, none of these agents altered systemic or renal hemodynamics in K-replete animals. Finally, because neither angiotensin antagonism nor prostaglandin inhibition alone decreased renal vascular resistance to levels sufficient to restore renal blood flow, studies were performed in which angiotensin and prostaglandins were both inhibited. Utilizing indomethacin and either saralasin or teprotide, renal blood flow was restored to normal values in K-deficient rats. Thus, we concluded that the increase in renal vascular resistance in K-deficient rats was caused by both angiotensin II and a vasoconstrictor product of prostaglandin endoperoxide metabolism, namely, thromboxane.

While the mechanism of renal vasoconstriction during K deficiency has been determined, the mechanism of systemic vasodilatation is not known. The decrease in systemic vascular resistance is of particular interest since it occurs in the setting of an increased cardiac output and activation of endogenous pressor systems. In this regard, plasma renin activity is increased, 14 and in preliminary studies we have found that arginine vasopressin levels (3.5 ± 0.2 vs 2.4 ± 0.2 pg/ml, p < 0.02) 33 are increased in K-deficient rats. Moreover, it is well recognized that K deficiency results in an increase in total body Na. 20, 37, 38

While there are no studies that have determined the reason for the increase in vasopressin in K deficiency, a number of possibilities seem likely. Although it is possible that K deficiency per se results in increased hormone biosynthesis, a more likely possibility is that the vasodilatation of K deficiency results in activation of arterial baroreceptors. Moreover, since K deficiency results in a renal concentrating defect, 35 it is possible that a subtle increase in plasma osmolality may lead to the osmotic stimulation of vasopressin release.

Two recent studies have examined the mechanism of increased renin secretion in the K-deficient rat. The three major intrarenal receptor mechanisms that control renin release are a vascular receptor, a renal tubular receptor (macula densa), and a beta adrenergic receptor. Luke et al. 36 have concluded that a renal tubular mechanism mediates the increase in renin secretion. A pivotal part of these studies was the observation that the administration of sodium chloride suppressed renin secretion in control rats but failed to suppress renin secretion in K-deficient animals. In earlier studies these investigators had shown that chloride transport was critical in suppressing renal tubular mediated renin release and that chloride transport may be decreased in K deficiency. Thus, they concluded that the failure of sodium chloride to suppress renin was caused by an inability to transport chloride in K-deficient animals.

In recent studies we concluded that the renal vascular receptor mediated the increase in renin. 37 For these studies, the isolated perfused kidney was utilized since ex vivo renal perfusion allows renin release to be studied in the absence of renal nerves and circulating factors such as catecholamines, which are known to directly increase renin secretion. Since renin production was increased in K-deficient perfused kidneys, stimulation of the renal beta receptor could be eliminated as the cause of hyperreninemia. Moreover, the increase in renin was associated with an increase in renal vascular resistance and a decrease in urine flow rate. Hence it was possible that either a vascular or a tubular mechanism could have accounted for the increase in renin. To determine if the decrease in distal nephron fluid delivery contributed to the increase in renin, delivery was enhanced by decreasing the albumin concentration of the perfusate. Just as Luke et al. 36 had shown, renin levels could not be suppressed by increasing distal nephron fluid delivery. Of importance, however, was the fact that in association with the enhanced delivery, vascular resistance remained increased in K-deficient kidneys. Moreover, when distal nephron fluid delivery was eliminated by perfusing with hyperoncotic albumin, a maneuver that eliminates glomerular filtration, renin levels remained increased and perfusion flow rate decreased in K-deficient kidneys. Since renin production by K-deficient kidneys was greater than renin production of control kidneys, even in the absence of distal nephron fluid delivery, the mechanism of hyperreninemia in the K-deficient perfused kidney occurred independent of changes of macula densa fluid delivery or transport.

To determine whether the increase in renal vascular resistance could have mediated the increased renin, nonfiltering kidneys were perfused with papaverine, a dilator of vascular smooth muscle. As seen in figure 4, papaverine caused a decrease in vascular tone in K-deficient kidneys. Moreover, the decrease in vascular tone was accompanied by a decrease in renin levels in K-deficient kidneys to values observed in control kidneys. Since papaverine had no direct effect on renin secretion, we concluded that the renal vascular receptor mediated the increased renin production in the K-deficient perfused kidney.

Although there is an increase in pressor hormone levels in K deficiency, the role of these hormones in the support of blood pressure has only recently been studied. Table 2 demonstrates the effect of angiotensin antagonism with saralasin in control rats and in rats maintained on a Na- or K-deficient diet for 14 days. Angiotensin inhibition resulted in a minimal depressor effect in control rats. As expected, Na-deficient rats had a very large decrease in mean arterial pressure. K-deficient animals had a substantially smaller decrease in pressure despite basal renin levels that were comparable to those of Na-deficient animals. Thus, while angiotensin clearly supports mean arterial pressure in Na deficiency, it has a relatively modest pressor role in K deficiency. This relative resistance to the pressor effect of angiotensin in K deficiency has been known.
for many years and results in blunted pressor sensitivity to exogenous angiotensin II. 40

Table 2 also demonstrates the effect of the administration of phenoxybenzamine, an alpha-adrenergic blocking agent. The hypotensive effect of alpha-adrenergic inhibition was comparable in both control and K-deficient rats. Moreover, since pressor sensitivity to norepinephrine is preserved in K-deficient animals, 39 the results suggest that the decrease in pressor sensitivity to angiotensin II is not caused by a generalized defect in smooth muscle reactivity but rather to a specific defect in angiotensin sensitivity. The results of recently completed studies are consistent with the conclusion that an alteration in the binding affinity of angiotensin II smooth muscle receptors mediates the decreased pressor sensitivity to angiotensin in K deficiency. 40

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Renin Activity (ng Al/ml/hr)</th>
<th>Reduction in MAP with teprotide (mm Hg)</th>
<th>Change in MAP with phenoxybenzamine (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.2 ± 0.7 (n = 8)</td>
<td>5.2 ± 1.9 (n = 7)</td>
<td>10.6 ± 1.9 (n = 5)</td>
</tr>
<tr>
<td>Na deplete</td>
<td>6.8 ± 0.8† (n = 7)</td>
<td>24.4 ± 3.4† (n = 6)</td>
<td></td>
</tr>
<tr>
<td>K deplete</td>
<td>8.5 ± 0.9† (n = 8)</td>
<td>11 ± 1.6‡† (n = 7)</td>
<td>12.1 ± 2.5 (n = 7)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SEM.

* p < 0.05 vs control.
† p < 0.01 vs control.
‡ p < 0.01 vs Na depleted.

Conclusions
The hemodynamic effects of alterations in serum K or in total body K content are only partially understood. In isolated preparations, acute K excess results in vasodilation, while acute K deficiency results in vasoconstriction. Chronic K excess results in a decrease in arterial pressure in hypertensive animals; no definitive conclusions exist on the effect of K excess in hypertensive man. The mechanism of the decrease in arterial pressure in hypertensive animals appears to be multifactorial, but at the present time it has never been dissociated from the natriuretic effect of K administration. Chronic K deficiency results in a decrease in arterial pressure in normal animals and may also decrease blood pressure in hypertensive animals. The mechanism of vasodilation appears to be a direct effect on the vascular smooth muscle since it occurs despite an increase in total body Na, renin, and arginine vasopressin. Further studies are warranted to determine whether alterations in total body K could be linked to the higher incidence of hypertension in the United States. Studies are also indicated to determine whether dietary or pharmacological manipulation of K would be useful in the treatment of hypertension.

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