The Effect of Potassium on the Occurrence of Petechial Hemorrhages in Renal Hypertensive Rabbits

By David B. Gordon, Ph.D. and Douglas R. Drury, M.D.

Administration of extra potassium to rabbits with renal hypertension reduces the incidence and severity of petechial hemorrhages. It also enables the animals to sustain higher blood pressure levels. Potassium apparently protects the vascular system to some extent against the damage caused by hypertension.

There have been several reports of a protective action by extra potassium in the diet against the toxic effects of DOCA administration. It not only protects against functional changes produced by large amounts of DOCA, such as muscle paralysis and irregular cardiac activity, but also against histological damage such as necrosis of cardiac muscle and possibly arteriolar necrosis. Since most of these toxic effects may be produced by low potassium diets and since DOCA has been shown to cause a loss of potassium from the body and from the tissues which become damaged, the conclusion has been drawn that the toxic action of DOCA is secondary to its diminution of intracellular potassium. The protective action of high potassium diets in DOCA intoxication is presumably due to a restoration of normal or near normal levels of intracellular potassium.

There have been occasional reports of a loss of potassium or a low serum potassium in malignant hypertension in human beings. In DOCA hypertension in the rat, potassium administration enhances the elevation of blood pressure but seems to improve rather than to deteriorate the general condition of these animals.

These findings led us to investigate the possibility of a protective action of potassium in renal hypertension. To the best of our knowledge, such an action has not previously been reported.

Methods

Female rabbits weighing between 2 and 5 Kg. were made hypertensive by means of renal artery constriction. A U-shaped silver clip of 0.55 mm. internal diameter was applied to the left renal artery and the light kidney was removed at the same operation.

Those animals which did not become hypertensive and those which did not survive more than two weeks postoperatively were excluded. The remaining animals were divided into two groups of 27 each. Animals of the experimental (K-treated) group were given a 1 per cent solution of KCl as sole drinking fluid. In 21 of these animals the potassium drinking was started two weeks postoperatively. In the other 6, it was begun two weeks prior to operation. In all 27, potassium drinking was continued for the duration of the survival of the animals. Animals of the control group were maintained on tap water pre- and postoperatively.

Blood pressures were taken at weekly intervals by the abdominal cuff method of MacGregor. Animals were not sacrificed, but were allowed to survive until they succumbed to their progressive hypertensive disease. Each animal was subjected to post-mortem examination as soon as possible after its death, usually within 4 to 16 hours, occasionally not for 1 or 2 days. Special attention was given to the occurrence of petechial or other hemorrhages and those on the intestine were graded on the basis of gross visual inspection—\(0 = \text{n}

These findings led us to investigate the possibility of a protective action of potassium in renal hypertension. To the best of our knowledge, such an action has not previously been reported.

From the Department of Physiology, School of Medicine, University of Southern California, Los Angeles, Calif.

This investigation was supported (in part) by a research grant (H-54-C7) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

Received for publication October 24, 1955.
of adjacent petechiae to form areas of gross hemorrhagic appearance and the intestinal contents were often bloody. In 20 of the 27 K-treated rabbits the daily intake of 1 per cent KCl was measured. In 9 controls and in 16 K-treated rabbits right kidney weights were measured at operation and left kidney weights were measured at autopsy in order to determine the extent of renal hypertrophy.

The two groups were compared on the basis of the occurrence and degree of petechial hemorrhages, survival, and blood pressures. In addition, the influence of a greater or lesser intake of potassium was examined and the possibility of an effect of potassium administration on renal hypertrophy was checked.

**RESULTS**

*Comparison of the groups as a whole: A summary of the results for both groups may be seen in table 1.* There are fewer animals with severe hemorrhages in the K-treated group (4 of 27 vs. 10 of 27). There are slightly more which have no hemorrhages in the K-treated group (8 of 27 vs. 5 of 27). One animal of the K-treated group is still alive after over 30 weeks of moderate hypertension.

Examination of the blood pressure records reveals no systematic action of potassium on the blood pressure of the renal hypertensive animals when the potassium chloride solution is first given. The rabbits' blood pressure may continue to rise, it may gradually level off or it may fall temporarily and then rise again. The same patterns of blood pressure levels are seen in the hypertensive rabbits maintained on tap water.

Nevertheless, a difference between the blood pressure levels of the 2 groups does exist. There are more animals which reach very high blood pressures in the K-treated group than in the control group. Only 3 or 11 per cent of the untreated animals reached systolic pressures of 200 mm. Hg or higher, while 13 or 48 per cent of the K-treated animals achieved such pressures. The distribution of maximum systolic pressures is shown in figure 1.

The survival of the K-treated rabbits is on the average, slightly longer than that of the animals of the control group (9.3 vs. 8.0 weeks). This difference is probably not significant.

*Comparison of animals surviving over four weeks postoperatively: It may be that those rabbits that died in four weeks or less were not much affected by the period of potassium drinking which then lasted only two weeks or less (excepting the rabbits given KCl prior to operation). Also, it is possible that the occurrence of severe vascular damage may depend on the duration as well as the severity of the hypertension. For these reasons, a comparison between K-treated and control rabbits was made, limited to those animals which survived more than 4 weeks postoperatively.*

Among these animals a somewhat sharper distinction exists between the experimental and control groups. Only 2 or 9 per cent of the K-treated animals had severe petechial hemorrhages while 9 or 43 per cent of the control animals had such hemorrhages. The average survival time again differs by a small number,
being 9.4 weeks for the control group and 10.6 weeks for the K-treated group. The data for the series of rabbits limited to those surviving over 4 weeks are shown in table 2.

Comparison of animals surviving over four weeks and arranged according to blood pressure levels attained: It has been suggested that vascular damage in renal hypertension is primarily a function of the blood pressure levels reached or sustained. From this standpoint, a valid comparison of vascular damage in K-treated and control groups may only be made between animals with similar elevations of blood pressure. Since each animal's pressure varies from week to week it is difficult to get strictly comparable groups of animals. A simple, but incomplete, solution to this problem is to compare animals with the same maximum systolic blood pressure. This method suffers from omission of the duration factor and the possibility of missing the true maximum between weekly readings, but it nevertheless provides a reasonable classification of the rabbits into blood pressure groups.

The degree of hypertension appeared to affect the efficacy of the potassium regime in reducing the hemorrhages as compared to controls with the same pressures. In the untreated group, the incidence of hemorrhages was independent of the maximum blood pressure reached, these occurring equally often at all blood pressure levels including the lowest (but still hypertensive levels). On the other hand, in the K-treated group there was a sharp distinction between rabbits that reached very high blood pressure levels and those that did not. Of the seven animals which never attained a systolic reading higher than 195 mm. Hg, 6 showed 0 hemorrhages at autopsy and the seventh is still alive at the time of this writing. Of the 15 K-treated rabbits reaching systolic pressures of 200 mm. Hg and higher, only 2 were free of hemorrhages at autopsy. However, even in the groups of animals between 200 and 239 mm Hg maximum, there were fewer animals with severe hemorrhages in the K-treated group than in the control group (2 of 11 compared to 5 of 12). No valid comparison may be made between K-treated animals with pressures of 240 mm. Hg and higher and control animals, since none of the control animals achieved such pressures. This fact may itself be indicative of a protective action of potassium.

The apparent discrepancy shown in the group of animals in the range 200 to 219 maximum pressure, in which there are five non-treated rabbits with 0 hemorrhages, brings up an interesting point. It was found that 3 out of these 5 rabbits (60 per cent) showed signs or symptoms suggestive of cardiac failure (such as head held tilted back, dyspnea, large quantities of fluid in abdomen and thorax, wet or heavy lungs). The number of rabbits showing such signs in the entire population of 54 rabbits was only 10 or 18.5 per cent. Of the 5 K-treated rabbits which showed 0 hemorrhages, 2 or 25 per cent presented signs suggesting cardiac failure. It may be that cardiac failure, or the condition resembling it in these rabbits, in some way decreases the likelihood of the occurrence of petechial hemorrhages.

Comparison of the animals with the highest potassium intake with those with the lowest potassium intake: Each rabbit drank an amount of 1 per cent KCl that varied daily. However, it was found that among the 20 rabbits whose daily intake was measured, some consistently drank more than others. As an arbitrary basis for comparison, the number of days on which drinking exceeded 600 cc. was divided by the total number of days on which drinking was measured, giving the fraction or percentages of "high drinking days." The animals can thus be divided into "high drinkers" (percentage over 25 per cent) and "low drinkers" (percentage lower than 10 per cent). Two rabbits fall into an intermediate group. The extent of hemor-

### Table 2.—Incidence of Hemorrhages in Limited Series* (81 animals in control group; 82 in Potassium-treated Group).

<table>
<thead>
<tr>
<th>Untreated</th>
<th></th>
<th>K-treated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>0 animals</td>
<td>++</td>
<td>2 animals</td>
</tr>
<tr>
<td>+</td>
<td>4 animals</td>
<td>+</td>
<td>4 animals</td>
</tr>
<tr>
<td>0</td>
<td>5 animals</td>
<td>0</td>
<td>8 animals</td>
</tr>
<tr>
<td></td>
<td>Alive</td>
<td>1 animal</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

* Over 4 weeks survival, +++, Severe & numerous hemorrhages; ++, Moderate hemorrhages; +, Few hemorrhages; 0, No hemorrhages.
rhages being compared, it is found that all high drinkers but one have only few or no hemorrhages while all but one of the low drinkers have moderate (+ + ) or severe (+ + + ) hemorrhages. There is also a tendency towards shorter survival in the low drinking group. These results are shown in table 3.

The difference between the extent of petechial hemorrhages in high and low potassium drinkers may be interpreted in two different ways. Either the protection against hemorrhages afforded by the potassium is proportional to the amount ingested or else rabbits with the more severe hypertensive disease tend to drink less of the potassium solution.

An additional finding deserves mention at this point. This is that the majority of the rabbits whose intake of KCl was measured daily showed a marked diminution in their daily intake for from 2 to 8 days before they died.* In fact we came to recognize this marked decrease in drinking as a reliable sign of impending death. Further investigation showed that this phenomenon was not limited to rabbits ingesting KCl but occurred also in the renal hypertensive rabbits drinking tap water.

Comparison of renal hypertrophy in potassium treated and in control hypertensive rabbits: It was found that in all rabbits after removal of the right kidney, a variable and often marked hypertrophy of the opposite kidney occurred in spite of the presence of a constricting clip on the renal artery. The possibility that any protective action the potassium exerted might be secondary to its effect on the size of the remaining kidney thus had to be considered. In a series of 25 animals, including 9 controls and 16 K-treated rabbits, the degree of hypertrophy of the left kidney was determined, using the weight of the right kidney (removed at operation) as indicating the pre-operative weight of the left. It was found that the average gain in weight of the left kidney during the post-operative survival period was 7.8 Gm. in the control rabbits and 7.7 Gm. in the K-treated rabbits. These values are practically identical. Therefore, one may conclude that the protective action of potassium administration is not dependent upon its effect upon renal hypertrophy.

DISCUSSION

The foregoing results lead to the same conclusion, namely that the administration of extra potassium to renal hypertensive rabbits protects them to a limited extent against vascular damage. It results in a decreased incidence and severity of petechial hemorrhages. It does not prevent their occurrence entirely except in those rabbits which never become severely hypertensive. This suggests that there may be an antagonism, insofar as vascular damage is concerned, between the effects of an elevated blood pressure and the action of an increased potassium intake.

It is to be noted that our evidence is based on the incidence of grossly visible hemorrhages and not on the occurrence of arteriolar necrosis or other damage which might be revealed by microscopic examination. Although it is logical to assume that the visible hemorrhages are the end result of arteriolar (and possibly capillary) necrosis and breakdown, Daniel and associ-
ates and others have found an occasional lack of correlation between the occurrence of macroscopic hemorrhages and the occurrence of arteriolar necrosis.

Paradoxically, the hypertensive rabbits given KCl in their drinking fluid tend to reach and sustain higher blood pressure levels than do similar rabbits maintained on tap water. This we interpret, not as a direct blood pressure elevating action of potassium, but as an indirect consequence of an action which permits the animal to develop higher blood pressures. Possibly the potassium serves to maintain the integrity of the blood vessels over a range of high blood pressures which, if developed by animals not given potassium would be rapidly fatal. Unpublished observations in our laboratory have shown that administration of 1 per cent KCl to normal non-operated rabbits is without any influence on their blood pressure levels.

Although potassium administration is to some degree effective in protecting against vascular damage it apparently affords little or no protection against the cause or causes of death in the renal hypertensive animal. This result is similar to that of Hellerstein and associates who found an antihemorrhagic effect of rutin in dogs with malignant hypertension with a lack of effect on their survival. Unlike our rabbits, their dogs all had very severe renal artery constriction with subsequent renal degeneration and necrosis and uremia. The causes of death in animals with milder degrees of renal artery constriction have not been fully investigated. The petechial hemorrhages themselves are probably not sufficiently destructive to be a cause of death, except perhaps when they are extremely severe on the gut and cause actual necrosis of portions of the intestine or when the brain is severely involved. They do not occur in the kidney, which is protected by the constricting silver clip from exposure to severely high blood pressures.

The chief theoretic importance of the finding that potassium administration may protect against vascular damage lies in its bearing upon prevailing theories as to the cause of such damage in hypertension. There are several theories which have been proposed, the main ones being: (1) that the vascular damage is simply a result of the elevated blood pressure to which the blood vessels are exposed; (2) that a combination of an elevated blood pressure and renal insufficiency is required, neither alone being a sufficient prerequisite for vascular damage; and (3) that an (unknown) renal deficiency alone may be a sufficient cause, with the hypertension being merely an aggravating factor. The latter theory has been supported by Muirhead and co-workers who also propose an interesting trio of hypotheses as to the possible deficiency of renal function which may be involved. These include: (1) an inadequate excretion of toxins, (2) a lack of regulation of intracellular electrolytes and (3) a disordered endocrine function of the kidney.

Our evidence upon the action of potassium appears to be related to the second or electrolytic concept proposed by Muirhead and co-workers. Unfortunately, we do not have any measurements of intracellular potassium levels, either in our hypertensive non-treated rabbits nor in those given extra potassium in their drinking fluid. It would seem logical to assume that if a deficiency of intracellular potassium exists in the vascular tissues of severely hypertensive animals and if this were related to the subsequent vascular breakdown, the administration of extra potassium in the diet might reverse both the deficiency and the breakdown. This is a purely speculative hypothesis and we have no direct evidence for it. Our results do not minimize the importance of an elevated blood pressure in the genesis of the vascular damage occurring in malignant hypertension but, in our opinion, this factor may very well act in conjunction with or in addition to another factor related to potassium metabolism.

SUMMARY

Two groups of rabbits were made hypertensive by renal artery constriction. One group was given extra potassium as 1 per cent KCl as the sole drinking fluid. The other group served as controls. It was found that the incidence of multiple hemorrhages on the intestines was reduced in the potassium-treated group. There was little correlation between the severity of the macroscopic hemorrhages and the severity of the hypertension in the control

GORDON AND DRURY 171
group. On the other hand, in the potassium group there was a correlation, only those rabbits whose pressures exceeded 200 mm Hg systolic having hemorrhages. Animals of the potassium group tended to reach and sustain higher blood pressures than those of the control group. This fact and the reduced incidence of hemorrhages in the potassium treated animals are taken as evidence of a protective action of potassium on the vascular system of hypertensive animals.

Acknowledgment
We wish to thank Mr. Yu Tsu Chao for his valuable technical assistance.

References
The Effect of Potassium on the Occurrence of Petechial Hemorrhages in Renal Hypertensive Rabbits

DAVID B. GORDON and DOUGLAS R. DRURY

Circ Res. 1956;4:167-172
doi: 10.1161/01.RES.4.2.167

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1956 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/4/2/167