Tissue Cations and Water in Arterial Hypertension

By Louis Tobian, Jr., M.D., and John T. Binion, B.S.

Human hypertensive subjects were found to have an increased sodium and water concentration in renal artery and psoas muscle. Hypertensive rats showed a high water content in their aortas. If the water and sodium content were increased in hypertensive arterioles as well as arteries, the swelling of the arteriolar walls would narrow the lumens enough to account for much of the increased peripheral resistance. Low sodium diets may alleviate hypertension by lowering the sodium and water contents in arteriolar walls toward normal values.

It is generally agreed that decreased lumen size of small arterioles is mainly responsible for the high arterial blood pressure in hypertensive disease. Chemical changes in the arteriolar wall undoubtedly play an important part in this process. However, arteriolar tissue samples are difficult to obtain for chemical studies. It was felt that chemical analysis of the larger muscular arteries might give an indication of chemical changes occurring in the arterioles, since both tissues are predominantly made up of vascular smooth muscle, and Wiggers believes that the walls of the larger arteries participate in the hypertensive process. In this study, other tissues were also analyzed in order to compare their chemistry with that of the muscular arteries.

Methods

Specimens of renal artery, psoas muscle, right auricle, bladder, and brain (frontal lobe) were obtained at the autopsy table and wiped free of blood. The adventitia was stripped from the renal arteries, leaving the intimal and medial layers for chemical analysis. Tissues were weighed, dried, defatted, and extracted with 0.75 normal nitric acid according to the method of Lowry and Hastings. In the sodium determination the sodium was ashed, precipitated, and washed according to the method of Lowry and Hastings and determined colorimetrically by the method of Hoffman and Osgood. Potassium was ashed, precipitated, and washed in Vycor tubes as described by Consolazio and Talbott and determined colorimetrically by the method of Shohl and Bennett. Magnesium was determined by the method of Michaels and associates.

Selection of Cases. Cases were classified either in the hypertensive or the normotensive group only when clinical and postmortem data left no doubt about their correct placement.

Results

In renal arteries of hypertensive patients the sodium content of the medial and intimal layers was 22 per cent higher and the water content 17 per cent higher than in arteries of normotensive subjects. (See table 1.)

Psoas muscle showed a 22 per cent higher sodium content and a 15 per cent higher water content in hypertensive patients than in normotensive subjects. These differences were statistically significant. (See table 2.)

There was no significant difference between the normotensives or hypertensives in potassium or magnesium content of arteries or muscle.

The sodium content of the brain in hypertensive patients was found to average 21 per cent higher than in normotensive subjects. However, the number of cases is small and there is one chance in six that the difference is due to chance. (See table 3.)

In right auricle and bladder no significant chemical differences between hypertensives and normotensives were found.

In figure 1 each point represents an individual subject, and the sodium content of renal artery is plotted against the water content. As would be expected from the osmotic activity of sodium, water and sodium contents tended to vary in the same direction.
It is to be expected that tissues would gain sodium after death as a result of diffusion. However, this process cannot account for the increased sodium in the renal artery and psoas muscle of the hypertensive group, since tissues were collected in this group an average of 5.4 hours after death, while tissues of the normotensive group were collected an average of 7.6 hours after death. If anything, the difference in sodium content might be even greater, were it not for the longer period of sodium diffusion after death in the normotensive group. Diffusion of sodium into renal artery tissue would be relatively slow because of the high sodium content of arteries.

The sodium and water content of renal artery and psoas muscle are not well correlated with the presence of edema in these subjects. There were several instances of high sodium and water content in subjects with no edema and instances of low sodium and water content in edematous subjects.

The data give no clue as to how much of the increased sodium and water in hypertensive artery and muscle is intracellular and how much extracellular.

Preliminary results also show that severely hypertensive rats have a 19 per cent higher water content in their aortas than normotensive rats (see table 4). The aorta of the rat has the histologic appearance of a small muscular

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<th>Table 1.—Analysis of Human Renal Artery (Media and Intima)*</th>
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<tr>
<td>13 Hypertensives</td>
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<td>15 Normotensives</td>
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<tr>
<td>Difference of means</td>
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<tr>
<td>Probability of chance difference between means</td>
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* Mean values and standard deviation.
† % Water = Wt. of water / Wt. of water + wt. of dry fat-free solids
‡ Per 100 Gm. of dry fat-free solids.

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<th>Table 2.—Analysis of Human Psoas Muscle*</th>
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<td>11 Hypertensives</td>
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<th>Table 3.—Analysis of Human Brain (Frontal Lobe)</th>
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<td>5 Hypertensives</td>
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<td>Probability of chance difference between means</td>
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* Per 100 Gm. of dry fat-free solids.
artery, being made up predominantly of smooth muscle.

It is of interest that Eichelberger has also found an increase in muscle sodium and water in Goldblatt hypertensive dogs.  

![Graph showing relation of water to sodium in the renal arteries of individual subjects.](image)

**FIG. 1.** Relation of water to sodium in the renal arteries of individual subjects.

**TABLE 4.—**Water Content of the Aorta of Hypertensive Rats (Gm. per 100 Gm. of dry fat-free solids)

<table>
<thead>
<tr>
<th>Normotensive (Average of 15 rats)</th>
<th>Mild Hypertensive (Average of 8 rats)</th>
<th>Severe Hypertensive (Average of 10 rats)</th>
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<td>175</td>
<td>184</td>
<td>208</td>
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![Diagram showing dimensions of an arteriole before and after swelling.](image)

**FIG. 2.** Dimensions of an arteriole before and after a 13 per cent swelling of the arteriolar wall. The decrease in lumen size would increase flow resistance 54 per cent.

**DISCUSSION**

It may be worthwhile to speculate about the possible causes and effects of the increased sodium and water content in renal artery associated with hypertension. It is quite possible that the increased water in the hypertensive arterial wall is there because of an increase in the number of intracellular osmotically active particles. This concept of intracellular metabolic alteration readily fits the fact that both artery and psoas muscle showed increased water and sodium contents. An increase in osmotically active intracellular sodium could account for a good part, but not necessarily all, of the increased arterial water content.

If the increased water concentration in hypertensive renal artery were also present in hypertensive arterioles, important results would follow. In the hypertensive renal artery, there was 17 per cent more water for each gram of solids than was found in normotensive renal artery. This amount of swelling with water would increase the mass of solids plus associated water 13 per cent in the hypertensive group.

In figure 2 there is depicted a normal arteriole 40 microns in diameter with a normal wall to lumen ratio of 1:2. If this wall were swelled 13 per cent as a result of more water, the radius of the lumen would decrease from 10 to 9 microns and the wall thickness would increase from 10 to 11.5 microns. According to Poiseille's equation, which states that flow resistance in capillary tubes varies inversely with the fourth power of the radius, this small decrease in lumen size would increase flow resistance 54 per cent in this hypothetic arteriole. If this were occurring in all the arterioles throughout the body, considerable hypertension would result.

The concept of the arteriolar wall swelled with water fits well with the observed fact that the blood pressure of a hypertensive patient can make large responses to either vasoconstricting or vasodilating stimuli. If the arteriolar muscle were hypercontracted, one might expect that further vasoconstriction would be somewhat limited and vasodilation responses would be disproportionately large.

The wall of the hypothetic "water-logged" arteriole in figure 2 is thickened to about the same degree as the walls of hypertensive arterioles in histologic muscle preparations. In benign hypertensive arterioles the wall to lumen ratio measured on slides averages 1:1.5 compared with a ratio of 1:2 in normotensive arterioles. Similarly, in our hypothetic "water-logged" arteriole, the wall to lumen ratio is 1:1.56 compared to the 1:2 ratio in the "normal" arteriole.
The fact that the renal artery of hypertensive patients contains abnormally large amounts of sodium may explain the effectiveness of drastic low sodium diets in lowering the blood pressure in hypertensive patients. If practically no sodium is supplied in the diet, individuals usually come into sodium balance eventually by a drastic reduction in the urinary sodium excretion. However, the body does lose about 200 mEq. of sodium before this balance is attained. Some of this deficit in total body sodium may be accounted for by a small contraction of extracellular fluid volume and blood volume. However, it seems quite unlikely that this small decrease in the volume of blood and extracellular fluid is the actual cause of the lowering of blood pressure. It is quite conceivable that a significant fraction of the deficit in total body sodium is lost from the walls of arteries and arterioles. As sodium was being lost from the arteriolar walls, the water osmotically bound by that amount of sodium would also be lost, provided other substances remained unchanged. As outlined above, this would effectively increase the lumen size of arterioles and thus decrease the level of arterial blood pressure.

Moreover, this concept may be applied in reverse. Sapirstein, Brandt, and Drury have reported hypertension in rats allowed to drink only a 2 per cent sodium chloride solution. Lenel, Katz, and Rodbard have reported an elevation of blood pressure in chickens on a high sodium intake. MeQuarrie and co-workers have produced definite hypertension in children during periods of feeding 30 to 60 Gm. of salt daily.

In all these cases, the high sodium intake could be increasing arteriolar sodium and water contents with resulting narrowing of the arteriolar lumens and arterial hypertension.

The concept also fits in with our previous experiments on bilaterally nephrectomized rats. Sixty-four per cent of these rats developed hypertension three days after bilateral nephrectomy, provided that they had free access to sodium in the diet. If sodium was withheld from the diet the day before and three days after the bilateral nephrectomy, hypertension appeared in only 2 per cent of the rats, even though there was no chance for these rats to become significantly depleted of sodium. It would appear that deficiency of the "renal anti-hypertensive function" cannot readily produce hypertension in these rats, unless sodium is supplied in the diet. Absence of sodium in the diet may prevent this type of hypertension by preventing an increase in the amount of arteriolar sodium and its osmotically bound water.

Raab and his associates have also shown that a low salt diet decreases the pressor response of hypertensive patients to norepinephrine and epinephrine. The elevated sodium in hypertensive artery may not only cause swelling of the wall with water, but may also make the artery more responsive to a given intensity of sympathetic vasoconstrictor nerve impulses.

Alterations in adrenal cortical steroid metabolism may or may not play a role in causing the elevated sodium and water in hypertensive artery and muscle. However, it is well known that hypertension produced by desoxy-corticosterone can be prevented by a drastically low sodium diet and augmented by a high sodium diet. This type of hypertension is mainly "humoral" and not neurogenic. In view of the strong influence of dietary sodium in this type of hypertension, it is quite conceivable that the walls of the peripheral arterioles contain excessive sodium and water, which would lead to increased peripheral resistance and hypertension. Moreover this same speculation would apply in the hypertension of toxemia of pregnancy, which is also markedly influenced by changes in the level of dietary sodium.

In the hypertensive subjects, the increased lateral hydrostatic pressure in the lumen of arteries undoubtedly increases the rate of fluid circulation from the lumen outward through the walls of the arteries. However, there is no reason to think that this heightened rate of circulation increases the amount of extracellular fluid in the walls of arteries. Moreover, the spaces between cells are not visibly widened in hypertensive arteries as they should be if there were considerable increases in extracellular water.
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**Summary**

1. Human hypertensive subjects showed an increased sodium and water concentration in renal artery and psoas muscle.

2. Preliminary results show that hypertensive rats have a high water content in their aortas.

3. The possible relationships between the above facts and arteriolar narrowing in hypertension are discussed.

**REFERENCES**


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