Venous responses to salt loading in hypertensive subjects

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ABSTRACT It has been previously suggested that salt loading produces structural changes of the arteries in hypertensive patients who respond to salt loading with a greater rise of blood pressure. This study examined the possibility that salt loading alters venous distensibility in hypertensive patients. Twenty-one patients with essential hypertension were placed on a low-sodium diet (70 meq) for 7 days and then were placed on a high-sodium diet (345 meq) for 7 days. Patients were arbitrarily divided into two groups based on the response of their blood pressure to salt loading: (1) those whose mean blood pressure increased by more than 10% while on the high-salt diet as compared with those on the low-salt diet (salt-responsive patients, n = 8) and (2) those whose mean blood pressure did not increase by more than 10% (salt-nonresponsive patients, n = 13). The venous pressure-volume relationship was determined in the forearm with a water-filled plethysmograph when patients were on the low- and high-salt diet. Venous pressure-volume curves were not different between salt-responsive and salt-nonresponsive patients while on the low-salt diet. High-salt intake shifted the curve toward the pressure axis for salt-responsive patients (p < .05) but not for salt-nonresponsive patients. Phentolamine, 1 mg administered intravenously for 5 min, did not significantly alter venous pressure-volume curves for either group while on the low- or high-salt diet. These results suggest that salt loading decreased venous distensibility in salt-responsive patients, which resulted from nonadrenergic mechanisms: structural changes of the veins could perhaps be included as one of these mechanisms.


Epidemiologic studies suggest that an excessive intake of salt contributes to the prevalence of essential hypertension in humans. However, the mechanisms by which an excessive intake of salt promotes hypertension in humans are not clear.

Recent studies have indicated that the response of blood pressure to salt loading varies among hypertensive patients. Studies by Kawasaki et al. and Fujita et al. indicated that patients who had a greater increase in blood pressure in response to salt loading (salt-responsive patients) excreted less sodium in urine, gained more weight, and had a greater increase in cardiac output during salt loading than did patients who did not have an increase in blood pressure or whose blood pressure increased less in response to salt loading (salt-nonresponsive patients). It was thus considered that the greater increase in blood pressure during salt loading in salt-responsive patients might be attributed to the greater increase in cardiac output that resulted from greater sodium retention.

We have recently suggested that in addition to greater sodium retention, an alteration of control of vascular resistance during salt loading may contribute to the salt-induced elevation of blood pressure in salt-responsive hypertensive patients. Salt loading increased vascular resistance in the forearm in salt-responsive patients but not in salt-nonresponsive patients. Furthermore, salt loading decreased maximal vasodilator capacity of the resistance vessels in the forearm in salt-responsive patients but did not alter it in salt-nonresponsive patients. These results suggested that salt loading produced structural changes of resistance vessels in the forearm in salt-responsive patients. Structural changes might involve the increased thickness of the vessel wall or the increase in sodium and/or water in the vessels.

It is known that there are abnormalities in veins as...
well as in arteries in humans and animals with spontaneous hypertension. There is a possibility that salt loading might produce changes in veins as well as in arteries in salt-responsive patients. If salt loading produces changes in veins and decreases venous distensibility, such changes might contribute to redistribution of venous blood from peripheral to cardiopulmonary circulation and thus might lead to the elevation of blood pressure by increasing cardiac output.

However, there are only a few studies that have examined the effects of salt loading on veins. Brown et al. reported that salt loading did not alter venous distensibility in hypertensive patients. However, most of their patients were salt-nonresponsive patients. It is possible that the venous responses to salt loading may differ between salt-responsive and salt-nonresponsive patients as did the arterial responses to salt loading.

The aim of this study was to examine whether salt loading altered venous distensibility in salt-responsive hypertensive patients. It has been implied that augmented neural mechanisms may contribute to salt-induced vasoconstriction in salt-responsive hypertensive patients. Accordingly, we also examined the role of α-adrenergic mechanisms in changes in venous distensibility in salt-responsive patients.

Methods

Twenty-one patients with essential hypertension (18 men and three women) were studied. Their ages ranged from 29 to 61 years old (average 47 ± 5, mean ± SE). All antihypertensive medications had been discontinued at least 10 days before admission. The patients were maintained on a 140 meq sodium diet for a week after admission, during which time patients underwent a routine work-up for hypertension, which included complete history and physical examination, urinalysis, urine culture, tests for serum and urinary electrolyte levels, creatinine clearance, and plasma renin activity, and rapid-sequence intravenous pyelograms. Plasma norepinephrine, aldosterone, and 24 hr urinary 17-hydroxycorticosteroids were measured as indicated. None of the patients had malignant hypertension. In no patient was there evidence of renal dysfunction, cardiac failure, or liver damage.

After a week of the 140 meq sodium diet, all patients were put on the 70 meq sodium diet for 7 days and then on the 345 meq sodium diet for 7 days. Blood pressure was measured by sphygmonanometer three times a day after the patients had been supine for 5 min. Mean blood pressure was calculated by adding diastolic pressure and one-third of pulse pressure.

Determination of venous distensibility. Venous distensibility was determined by obtaining venous pressure-volume curves. A single-chamber water-filled plethysmograph was used for recording changes in volume of a segment of the left forearm. Subjects wore light clothing and felt comfortably warm at a room temperature of 18° to 22° C.

The left forearm was enclosed in an acrylic plastic plethysmograph. Water was added to 26 cm above the upper aspect of the forearm. Under these conditions the external water pressure initially collapsed the veins, but the arterial inflow caused the venous pressure to reach a level slightly higher than that of the external water pressure. The difference between the pressure within the veins and the external water pressure surrounding them is the distending or transmural pressure. Venous pressure was measured through a polyethylene tube inserted into a superficial vein in the segment of the forearm enclosed in the plethysmograph. Transmural venous pressure was measured by placing the reference level of the pressure transducer at the level of the surface of the water in the plethysmograph. Transmural venous pressure in patients at rest under these conditions was less than 1.5 mm Hg. The volume of blood in the vessels in the forearm at this low transmural venous pressure is approximately 1.3 ml/100 g of tissue, and under resting conditions, transmural venous pressure and volume are constant and reproducible in a given subject.

Changes in the volume of blood in the forearm were recorded during stepwise increases in transmural venous pressure to 30 mm Hg by inflating a cuff on the arm proximal to the plethysmograph (figure 1). Transmural venous pressure was increased slowly to minimize nonuniform filling of the veins and was held constant at each step until changes in the volume of blood in the forearm became stable (figure 1). Changes in the venous volume were reflected by the changes in the volume of blood in the forearm, which were measured by recording changes in the height of water. Increases in volume in response to congestion of the forearm take place primarily in vessels in which resting

FIGURE 1. Recordings of the changes in venous volume in the forearm during a stepwise increase in transmural venous pressure from the baseline value (about 1 mm Hg) to 30 mm Hg.
pressure is less than 10 mm Hg. Venous pressure-volume curves were constructed by plotting changes of volume of blood in the forearm (ml/100 ml of forearm volume) against corresponding levels of transmural venous pressure.

To investigate the contribution of α-adrenergic mechanisms to venous distensibility, measurements of venous distensibility were obtained before and after intravenous administration of phentolamine at a rate of 1 mg/min for 5 min in five salt-responsive patients and eight salt-nonresponsive patients. It has been previously shown that this dose of phentolamine is sufficient to block the reflex venoconstriction in response to deep inspiration when the occluded-vein technique is used. To determine if the external water pressure of 20 mm Hg was sufficient to collapse the veins under resting conditions, we measured the changes in the volume of blood in the forearm in two salt-responsive patients during low- and high-salt intake as the external water pressure was increased from 0 mm Hg (the height of the water column at the level of the upper part of the forearm) to 27 mm Hg.

Protocol. Blood pressure and body weight were measured every day during low- and high-salt intake. Body weight was measured in the morning after voiding. Average values of mean blood pressures recorded at the seventh day of low- and high-salt intake were compared. Patients were arbitrarily divided into the following two groups based on response of their blood pressure to salt loading: (1) patients whose average mean blood pressure on the seventh day of the high-salt diet exceeded by 10% or more that on the seventh day of the low-salt diet (salt-responsive patients), and (2) those whose average mean blood pressure during the high-salt diet either decreased or exceeded by less than 10% that during the low-salt diet (salt-nonresponsive patients). On the seventh day of low- and high-salt intake, the venous pressure-volume relationship was examined before and after intravenous phentolamine. In addition, we examined vascular resistance in the forearm in patients at rest and during peak reactive hyperemia after 10 min of arterial occlusion (maximal vasodilator capacity), and we measured serum and urinary electrolyte levels and plasma renin activity. The results of vascular resistance in the forearm, maximal vasodilator capacity, excretion of urinary electrolytes, and plasma renin activity were reported separately.

Statistical analysis. Student’s t test was used for comparisons between groups, and the paired t test was used for comparison between two salt diets within the same group. We considered p ≤ .05 as a statistically significant difference.

Results

Eight and 13 patients were placed into the salt-responsive and the salt-nonresponsive groups, respectively. During the low-salt diet, mean blood pressure of salt-responsive patients tended to be higher, but not significantly, than that of salt-nonresponsive patients (120 ± 9 mm Hg vs 108 ± 5 mm Hg). High-salt intake increased mean blood pressure (p < .01) in salt-responsive patients (138 ± 9 mm Hg while on the high-salt diet) but not in salt-nonresponsive patients (108 ± 5 mm Hg while on the high-salt diet).

Body weight increased in salt-responsive patients while on the high-salt diet (50.1 ± 4.2 kg vs 51.2 ± 4.4 kg, p < .01), but did not change in salt-nonresponsive patients (61.0 ± 4.3 kg vs 60.9 ± 4.3 kg).

The volume of blood in the forearm enclosed in the plethysmograph was not different during the low- and high-salt diet either in salt-responsive patients (449 ± 48 ml while on the low-salt diet and 455 ± 61 ml while on the high-salt diet) or in salt-nonresponsive patients (504 ± 27 ml while on the low-salt diet and 504 ± 37 ml while on the high-salt diet).

The venous pressure-volume relationships in salt-responsive and salt-nonresponsive patients while on the low- and high-salt diet are shown in table 1 and figure 2. The changes in volume of blood in the forearm at each level of transmural venous pressure were not significantly different between the two groups while on the low-salt diet. However, the high-salt diet decreased the changes in transmural venous pressure of the forearm by 10, 15, 20, and 30 mm Hg (table 1 and figure 2) in salt-responsive patients but not in salt-nonresponsive patients. Thus, the high-salt diet decreased venous distensibility in salt-responsive patients but not in salt-nonresponsive patients.

Phentolamine did not significantly alter venous distensibility in either group of patients while on the low- or high-salt diet (table 2). Thus, after phentolamine, venous distensibility remained significantly lower in salt-responsive patients when on the high-salt diet than when they were on the low-salt diet.

When the external water pressure was increased from 0 to 12 mm Hg, the volume of blood in the forearm decreased progressively (figure 3). However, increasing external water pressure above 12 mm Hg did not produce an appreciable decrease in the volume of blood in the forearm.

Discussion

In this study we arbitrarily divided patients with essential hypertension into two groups, salt-responsive and salt-nonresponsive; the division was based on response of blood pressure to salt loading, and we examined the possible difference in venous responses to salt loading between the two groups. The results of this study indicate that the magnitudes of increase in venous volume to stepwise increases of transmural venous pressure were less during high-salt intake as compared with those during low-salt intake in salt-responsive patients but not in salt-nonresponsive patients.

The validity of the equilibration technique for the measurement of venous distensibility in man has been extensively studied and discussed. A discussion of a few points are relevant to the present study.

The venous pressure-volume relationship is not linear but hyperbolic (figure 2). Therefore, when the equilibration technique is used for the measurement of
**TABLE 1**

Changes in forearm volume (ml/100 ml of forearm volume) at graded transmural venous pressure (mm Hg) during low- and high-salt diet

<table>
<thead>
<tr>
<th>Transmural Venous Pressure (mm Hg)</th>
<th>Low-salt diet</th>
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<tr>
<td></td>
<td>5</td>
<td>10</td>
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<tr>
<td>Salt-responsive patients</td>
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<tr>
<td>1</td>
<td>1.8</td>
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<td>2</td>
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<tr>
<td>8</td>
<td>2.0</td>
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<tr>
<td>Mean</td>
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<td>±SE</td>
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<td>±0.1</td>
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<tr>
<td>Salt-nonresponsive patients</td>
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<td></td>
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<tr>
<td>1</td>
<td>1.4</td>
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<tr>
<td>±SE</td>
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*p < .05 low- vs high-salt diet.

**p < .01 low- vs high-salt diet.

**FIGURE 2.** Venous pressure-volume curves. The values for salt-responsive patients (n = 8) are shown in circles and those for salt-nonresponsive patients (n = 13) in triangles. Solid lines indicate the curves during low-salt diet and broken lines during high-salt diet. The curves during low-salt diet were not different between the two groups. High-salt intake shifted the curve toward the pressure axis (* = p < .05 and ** = p < .01, low- vs high-salt diet) in salt-responsive patients but not in salt-nonresponsive patients. The standard errors of the values are given in table 1.
TABLE 2
Changes in forearm volume (ml/100 ml of forearm volume) at graded transmural venous pressure (mm Hg) before and after phentolamine

<table>
<thead>
<tr>
<th></th>
<th>Low-salt diet</th>
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<th>High-salt diet</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>1.7 ± 0.1</td>
<td>2.6 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>3.3 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>1.5 ± 0.1</td>
<td>2.0 ± 0.2B</td>
<td>2.5 ± 0.3B</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>1.7 ± 0.1</td>
<td>2.7 ± 0.2</td>
<td>3.2 ± 0.3</td>
<td>3.6 ± 0.3</td>
<td>4.1 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>2.1 ± 0.2B</td>
<td>2.5 ± 0.3B</td>
</tr>
<tr>
<td>Salt-responsive</td>
<td>(n = 5)</td>
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<tr>
<td></td>
<td>Before</td>
<td>1.9 ± 0.3</td>
<td>2.8 ± 0.4</td>
<td>3.3 ± 0.4</td>
<td>3.6 ± 0.4</td>
<td>4.1 ± 0.5</td>
<td>1.9 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>3.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>2.1 ± 0.3</td>
<td>2.9 ± 0.4</td>
<td>3.4 ± 0.5</td>
<td>3.8 ± 0.5</td>
<td>4.4 ± 0.5</td>
<td>1.9 ± 0.3</td>
<td>2.8 ± 0.4</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Salt-nonresponsive</td>
<td>(n = 8)</td>
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</table>

Values were not different before and after phentolamine during low- or high-salt diet in either group of patients.

Low- vs high-salt diet, p < .01.

venous distensibility, it is most important that the venous pressure-volume relationship is examined from the same reference point or the baseline of the venous volume and transmural venous pressure. If the baseline venous volume and transmural venous pressure were higher during high-salt intake as compared with those during low-salt intake, the observed shift of the venous pressure-volume curve toward the pressure axis during high-salt intake might have resulted from a higher baseline venous volume. However, this possibility is unlikely since the segments of forearm veins from which the venous pressure-volume relationship was examined should have been nearly collapsed by the external water pressure of 20 mm Hg. It has been shown that the baseline venous volume and transmural venous pressure under these conditions are constant and reproducible in a given subject.

In this study, we examined whether the external water pressure of 20 mm Hg was in fact sufficient to reduce the volume of blood in the forearm to the minimal and constant level during high- as well as low-salt intake in two salt-responsive patients. We measured volume of blood in the forearm as the external water pressure was increased stepwise to 27 mm Hg. As shown in figure 3, a stepwise increase in the external water pressure produced a large decrease in the volume of blood in the forearm, thus a decrease in the venous volume; however, increasing the external water pressure above 12 mm Hg did not produce an appreciable further decrease in the baseline forearm volume when patients were on either the low- or high-salt diet. These results suggest that under the external water pressure of 20 mm Hg, the forearm venous volume was reduced to the minimal baseline level in patients while on the high- as well as low-salt diet. The baseline transmural venous pressure under the external water pressure of 20 mm Hg was about 1 mm Hg and was not different between low- and high-salt diet in either group, nor between the two groups during either diet (figure 2). Although the baseline venous volume is not known, it

FIGURE 3. Changes in the baseline forearm volume during a stepwise increase in external water pressure in a salt-responsive patient during low- (closed circles) and high- (open circles) salt diet. Increasing the external water pressure from 0 to 12 mm Hg decreased forearm volume but further increases in external water pressure did not produce a further decrease in the baseline forearm volume during low- or high-salt diet.

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is reasonable to assume that the baseline venous volume was similar during low- and high-salt diet since the veins were collapsed by the external water pressure and baseline transmural venous pressure was minimal and not different between the two diets.

Thus, we consider that the results are unlikely to be explained by the difference in the baseline venous volume and transmural venous pressure, but we suggest that high-salt intake decreased venous distensibility in salt-responsive patients but not in salt-nonresponsive patients.

Mechanisms by which high-salt intake decreased venous distensibility in salt-responsive patients are unclear. Since phentolamine in a dose that was sufficient to prevent reflex venoconstriction did not alter venous distensibility, the salt-induced decrease in venous distensibility in salt-responsive patients was not related to adrenergic mechanisms. It is unlikely that angiotensin or vasopressin are responsible for the decrease in venous distensibility since they do not produce venoconstriction. Although serotonin constricts veins, serotonin is not implicated in hypertension. It is possible that humoral factors that act on membrane Na⁺⁻K⁺ ATPase might be involved. Such humoral factors might decrease venous distensibility directly by increasing venous tone or indirectly by increasing intracellular contents of sodium and water.

The decreased venous distensibility might be related to structural abnormalities of the veins. The results of the effects of the high-salt diet on vascular resistance of the forearm in these patients have been reported separately, and it was suggested that the high-salt diet produced structural changes in the resistance vessels in salt-responsive patients but not in salt-nonresponsive patients. It may be possible that structural changes developed in veins as well as in arteries during the high-salt diet in salt-responsive patients.

A recent study in rats supports the possibility that high-salt intake may produce structural changes in the veins. High-salt intake decreased venous distensibility in spontaneously hypertensive rats but not in normotensive Wistar Kyoto rats. Decreased venous distensibility in spontaneously hypertensive rats during high-salt intake persisted during sodium nitroprusside infusion. Structural changes of the veins during a high-salt diet might involve increased water, sodium, and potassium content of veins or decreased compliance of interstitial space.

It is not clear whether the decreased venous distensibility found in salt-responsive patients while on a high-salt diet contributed to the salt-induced increase in blood pressure. Fujita et al. previously suggested that the increase in blood pressure in salt-responsive patients while on a high-salt diet might be attributed to the increase in cardiac output. The decreased venous distensibility might have contributed to redistribution of venous blood from periphery to cardiopulmonary circulation and thus to the increase in cardiac output. It is conceivable that with an associated alteration in control of vascular resistance and reduced excretion of renal sodium, the decreased venous distensibility might contribute to the salt-induced elevation of blood pressure in salt-responsive hypertensive patients.

In summary, the high-salt diet produced changes in capacitance vessels as well as resistance vessels in salt-responsive patients but not in salt-nonresponsive patients. Venous distensibility was decreased during the high-salt diet in salt-responsive hypertensive patients but not in salt-nonresponsive patients. The decreased venous distensibility was produced by nonadrenergic mechanisms that may have included structural changes in the veins.

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References


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