Characteristics of Responses to Salt Loading and Deprivation in Hypertensive Subjects

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SUMMARY. The mechanisms by which high salt intake increases vascular resistance in hypertensive humans are not clear. This study examined the possibility that salt loading produces structural changes of the forearm resistance vessels in hypertensive patients. Seventeen patients with essential hypertension were given 7 days of 70 mEq and 345 mEq sodium diet. Patients were arbitrarily divided into two groups based on blood pressure response to salt loading: those whose mean blood pressure increased by more than 10% during high salt diet as compared to those on a low salt diet (salt-responsive patients, n = 8) and those who did not increase by more than 10% (salt-nonresponsive patients, n = 9). To determine whether there were structural vascular changes of the forearm resistance vessels during salt loading, we examined maximal vasodilator capacity of the forearm resistance vessels during low and high salt diets by measuring minimal forearm vascular resistance (P < 0.01) and decreased maximal vasodilator capacity (P < 0.01) in salt-responsive patients but did not alter them in salt-nonresponsive patients. Forearm vascular responses to ice on the forehead or to intravenous phentolamine (10 mg) were augmented (P < 0.01) during the high salt diet in both groups, but more in salt-responsive patients than in salt-nonresponsive patients (P < 0.01). These results are consistent with the view that, in hypertensive patients who responded to salt loading with a greater rise of blood pressure, salt loading produced structural changes of the forearm resistance vessels and structural vascular changes contributed to the salt-induced increase in forearm vascular resistance. (Circ Res 51: 457-464, 1982)

EPIDEMIOLOGICAL studies suggest that excess salt intake contributes to the prevalence of essential hypertension in humans (Freis, 1976). However, the mechanisms by which excess salt intake alters control of vascular resistance and promotes hypertension in humans are not clear.

Studies in animals have suggested several mechanisms by which excess salt might increase vascular resistance and blood pressure. These include augmentation of sympathetic activity and release of norepinephrine from adrenergic nerve endings (De Champlain et al., 1968; Takeshita and Mark, 1978; Takeshita et al., 1979), autoregulation of blood flow (Coleman et al., 1971), alterations in transmembrane ionic exchange in vascular muscle (Bohr et al., 1969; Blaustein, 1977); salt-sensitive humoral factors (Dahl et al., 1967; Haddy and Overbeck, 1976), and, finally, structural changes in blood vessels (Tobian and Binion, 1952; Folkow, 1971; Overbeck, 1979; Limas et al., 1980).

Of particular interest is a recent study by Limas et al. (1980) which demonstrated that salt loading produced significant thickening of the vessel wall in the intrarenal arteries as well as in the aorta in spontaneously hypertensive rats. Structural vascular abnormality preceded the salt-induced acceleration of hypertension, which suggested that salt-induced structural vascular abnormality in spontaneously hypertensive rats was not secondary to the elevation of blood pressure. Excess salt intake might also increase the wall-to-lumen ratio of the resistance vessels by increasing salt and water content in the vessels (Tobian and Binion, 1952; Folkow, 1971). These structural vascular changes produced by excess salt intake could contribute importantly to the increase in vascular resistance during salt loading.

Despite the great interest in the role of salt in the pathogenesis of essential hypertension in humans, only few studies have examined control of vascular resistance during excess salt intake in humans. Available information suggests that excess salt intake may augment neurogenic vasoconstriction in salt-sensitive humans (Mark et al., 1975; Fujita et al., 1980). However, the possibility that excess salt intake alters the wall-to-lumen ratio of the resistance vessels has not been examined in humans.

Recent studies indicate that blood pressure response to salt loading varies among hypertensive patients (Kawasaki et al., 1978; Fujita et al., 1980; Sullivan et al., 1980). In the present study, we examined the hypothesis that the altered wall-to-lumen ratio of the resistance vessels may contribute to the increase in vascular resistance in hypertensive patients whose blood pressure becomes elevated during salt loading. The altered wall-to-lumen ratio of the resistance vessels can be assessed physiologically by measuring vascular resistance during maximal vasodilation (Folkow et al., 1958; Conway, 1963; Berecek and Bohr, 1977). In this study, we examined maximal vasodilator capacity during peak reactive hyperemia in patients with essential hypertension during low
and high salt intake, to determine whether excess salt intake alters maximal vasodilator capacity in salt-responsive hypertensive patients.

Methods

Seventeen patients with essential hypertension (13 men and four women) were studied. All antihypertensive medications had been discontinued at least 2 weeks prior to admission. All patients were maintained on 140 mEq sodium diet for a week after admission, during which period patients underwent a routine work-up for hypertension including complete history and physical examination, urinalysis, urine culture, serum and urinary electrolytes, creatinine clearance, plasma renin activity, and rapid-sequence intravenous pyelograms. Plasma norepinephrine, aldosterone, and 24-hour urinary 17-hydroxycorticosteroids were measured as indicated. None of the 17 patients had malignant hypertension. In no patient was there evidence of renal dysfunction, of cardiac failure, or of liver damage.

After a week of 140 mEq sodium diet, all patients were put on 70 mEq sodium diet for 7 days and then on 345 mEq sodium diet for 7 days. Potassium intake was maintained at 55 mEq/day throughout the study. Blood pressure was measured by sphygmomanometer four times a day, after the patients had been supine for 5 minutes. Blood pressure was measured in the morning while the patient was in bed, and before any physical activity. Mean blood pressure was calculated by adding diastolic pressure and one-third of pulse pressure.

Measurements of Forearm Blood Flow

Forearm blood flow was measured using a mercury-in-Silastic strain gauge plethysmograph with a venous occlusion technique (Greenfield et al., 1963). The strain gauge was placed approximately 5 cm below the antecubital crease. The pressure in the venous occlusion or congestive cuff was 40 mm Hg (Folkow et al., 1958). Circulation to the hand was arrested by inflating a cuff around the wrist during determination of forearm blood flow. The blood pressure was measured in the opposite arm with a sphygmomanometer. Forearm vascular resistance was calculated by dividing mean arterial pressure (diastolic pressure plus one-third of pulse pressure in mm Hg) by blood flow (ml/min per 100 ml of forearm volume); these values are expressed as units throughout this report.

Control forearm blood flow was measured after at least 15 minutes of rest following placement of the instruments. Control blood flow was taken as the average of five to seven flow measurements made at 15-second intervals.

Measurements of Maximal Vasodilator Capacity of Forearm Resistance Vessels

Maximal vasodilator capacity was examined by obtaining minimal forearm vascular resistance during peak reactive hyperemia following release of 10 minutes of arterial occlusion (Takeshita and Mark, 1980). To produce reactive hyperemia, blood flow to the forearm was occluded by inflating a cuff on the upper arm to suprasystolic pressure. After release of arterial occlusion, forearm blood flow was measured 7 seconds after release and every 15 seconds thereafter for 2 minutes. Peak blood flow after release of arterial occlusion and blood pressure measured in the opposite arm were used to calculate minimal forearm vascular resistance. It has been shown previously that maximal vasodilation of forearm resistance vessels is achieved during peak reactive hyperemia following 10 minutes of arterial occlusion (Takeshita and Mark, 1980).

Measurements of Forearm Vascular Responses to Ice and to Phentolamine.

We examined the responses of forearm vascular resistance to ice on the forehead for 45 seconds and to intravenous phentolamine, 10 mg by bolus. Blood pressure was measured at the opposite arm by sphygmomanometer before and at the termination of ice on the forehead, and before and every 30 seconds after an intravenous injection of phentolamine until blood pressure returned to the resting level. Forearm blood flow was recorded every 15 seconds. Forearm vascular resistance was calculated before and at the termination of cold stimulus. Forearm vascular resistance during phentolamine was calculated before and at every 30 seconds after the injection of phentolamine, and minimal vascular resistance obtained after phentolamine was compared with that before phentolamine.

Protocol

Blood pressure and body weight were measured every day during low and high salt intake. Average values of

![Figure 1](http://circres.ahajournals.org/)

**FIGURE 1.** The per cent increase of the mean blood pressure during high salt diet. In this and the following figures, closed circles represent data in the salt-responsive patients and open circles those in the salt-nonresponsive patients. Circles with bars indicate mean ± SEM. High salt intake increased mean blood pressure in the salt-responsive patients (P < 0.01) but not in the salt-nonresponsive patients.
mean blood pressures recorded at the 7th day of high and low salt diet were compared. As in the previous studies (Kawasaki et al., 1978; Fujita et al., 1980), patients were arbitrarily divided into two groups based on blood pressure response to salt loading; patients whose average mean blood pressure value on the 7th day of the high salt diet exceeded by 10% or more that on the 7th day of the low salt diet (salt-responsive patients), and those whose average mean blood pressure during high salt diet exceeded by less than 10% that during low salt diet or whose pressure decreased (salt-nonresponsive patients) (Fig. 1). Body weight was measured in the morning after voiding.

On the 7th day of low and high salt intake, we measured serum electrolytes, urinary excretion of sodium, potassium and creatinine, and plasma renin activity. Plasma renin activity was measured by radioimmunoassay by the modification of the method of Haber et al. (1969). At the 7th day of low and high salt intake, we also examined forearm vascular resistance at rest and during peak reactive hyperemia after 10 minutes of arterial occlusion, and forearm vascular responses to ice on the forehead and to phenolamine.

Calculations and Statistical Analysis
Calculation of forearm blood flow from the records was done by an individual (T. H.) who was not informed whether a record was obtained from a salt-responsive or a salt nonresponsive subject.
Paired and unpaired Student's t-tests were used for a statistical analysis, and P < 0.05 was considered significant. Data are shown as mean ± SEM.

Results
Eight and nine patients fell into the salt-responsive and the salt-nonresponsive group, respectively (Fig. 1). Table 1 summarizes clinical and laboratory findings of patients on admission. The values listed in Table 1 indicate no difference between the salt-responsive and the salt-nonresponsive patients on admission. Blood urea nitrogen, serum creatinine, and hemoglobin were normal in all patients.

Metabolic and Humoral Effects (Table 2)
High salt diet increased urinary excretion of sodium (P < 0.01) and decreased plasma renin activity (P < 0.05) in both groups. There was no difference in urinary excretion of sodium between the two groups during low salt diet. Urinary excretion of sodium during high salt diet tended to be lower, but not significantly, in salt-responsive patients, than in salt-nonresponsive patients. Plasma renin activity was higher (P < 0.01) during low salt diet but not during high salt diet in salt-nonresponsive patients than it was in salt-responsive patients. Urinary excretion of potassium and serum sodium and potassium was not changed by high salt diet in salt-responsive and salt-nonresponsive patients, and was not different between the two groups.

Body weight increased during high salt diet in salt-responsive patients (P < 0.01) but not in salt-nonresponsive patients.

Hemodynamic Effects (Table 3)

Mean BP and Resting Forearm Dynamics
High salt diet increased mean BP in salt-responsive patients (P < 0.01) as a group but not in salt-nonres-

### Table 1

<table>
<thead>
<tr>
<th>Clinical and Laboratory Findings on Admission</th>
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<tr>
<td>( n )</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Blood pressure</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/100 ml)</td>
</tr>
<tr>
<td>Serum creatinine (mg/100 ml)</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
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</tbody>
</table>

None of the values are different between the salt-sensitive and the salt-resistant patients. Data are shown as mean ± SEM.

### Table 2

<table>
<thead>
<tr>
<th>Metabolic Effects</th>
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<tr>
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<tr>
<td>Body weight (kg)</td>
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<tr>
<td>Plasma sodium (mEq/liter)</td>
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<tr>
<td>Plasma potassium (mEq/liter)</td>
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<tr>
<td>Urinary sodium excretion (mEq/day)</td>
</tr>
<tr>
<td>Urinary potassium excretion (mEq/day)</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml per hr)</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SEM.
* Indicates P < 0.05 (low salt vs. high salt).
† Indicates P < 0.01 (low salt vs high salt).
‡ Indicates P < 0.01 (salt-sensitive vs. salt-resistant).
TABLE 3

Hemodynamic effects

<table>
<thead>
<tr>
<th></th>
<th>Salt-responsive</th>
<th>Salt-nonresponsive</th>
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<tbody>
<tr>
<td></td>
<td>Low salt (n = 8 ~ 9)</td>
<td>High salt (n = 8 ~ 9)</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>116 ± 7†</td>
<td>130 ± 8*‡</td>
</tr>
<tr>
<td>Resting forearm blood flow (ml/min per 100 ml)</td>
<td>5.4 ± 0.8</td>
<td>3.7 ± 0.4*</td>
</tr>
<tr>
<td>RESTING Forearm vascular resistance (units)</td>
<td>25 ± 4</td>
<td>37 ± 2†</td>
</tr>
<tr>
<td>Response to ice (n = 6)</td>
<td>± Mean blood pressure (mm Hg)</td>
<td>4 ± 3</td>
</tr>
<tr>
<td></td>
<td>Δ Forearm vascular resistance (units)</td>
<td>5 ± 1</td>
</tr>
<tr>
<td></td>
<td>Δ Forearm vascular resistance (%)</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Responses to phentolamine (n = 6)</td>
<td>-12 ± 2</td>
<td>-22 ± 7</td>
</tr>
<tr>
<td></td>
<td>Δ Mean blood pressure (mm Hg)</td>
<td>-8 ± 0.3‡</td>
</tr>
<tr>
<td></td>
<td>Δ Forearm vascular resistance (units)</td>
<td>-30 ± 6‡</td>
</tr>
<tr>
<td></td>
<td>Δ Forearm vascular resistance (%)</td>
<td>-45 ± 4*</td>
</tr>
<tr>
<td>Minimal forearm vascular resistance (units)</td>
<td>1.9 ± 0.1</td>
<td>2.7 ± 0.2*†</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SEM.
† Indicates P < 0.01 (low salt vs. high salt).
‡ Indicates P < 0.01 (salt-sensitive vs. salt-resistant).

Salt-responsive patients. Mean BP was higher in salt-responsive patients than in salt-nonresponsive patients during low (P < 0.05) as well as high salt diet (P < 0.01), even though blood pressure on admission was not significantly different between the two groups.

High salt diet decreased forearm blood flow (P < 0.01) and increased forearm vascular resistance (P < 0.01) in salt-responsive patients, but it did not change them in salt-nonresponsive patients. Forearm blood flow and vascular resistance were not different between the two groups during low salt diet. During high salt diet, forearm blood flow was lower (P < 0.01) and vascular resistance was higher (P < 0.01) in salt-responsive patients than they were in salt-nonresponsive patients.

Maximal Vasodilator Capacity

High salt diet significantly increased minimal forearm vascular resistance during peak reactive hyperemia following 10 minutes of arterial occlusion in salt-responsive patients (P < 0.01), whereas, in salt-nonresponsive patients, high salt diet did not alter minimal forearm vascular resistance (Fig. 2).

Responses to Ice on the Forehead and to Phentolamine

During low salt diet, the increase of forearm vascular resistance in response to ice on the forehead was not different between the two groups (Fig. 3), but the decrease of forearm vascular resistance in response to phentolamine was greater (P < 0.05) in salt-responsive patients than in salt-nonresponsive patients (Fig. 4).

Forearm vascular response to ice on the forehead was greater during high than during low salt diet in both salt-responsive (P < 0.01) and salt-nonresponsive patients (P < 0.01) (Fig. 3). The extent of aug-

FIGURE 2. Minimal forearm vascular resistance during peak reactive hyperemia after 10 minutes of arterial occlusion. High salt intake increased minimal forearm vascular resistance in the salt-responsive patients (P < 0.01) but not in the salt-nonresponsive patients.
The changes in forearm vascular resistance in response to ice on the forehead during low and high salt diet. High salt diet augmented forearm vascular responses to ice in the salt-responsive as well as in the salt-nonresponsive patients ($P < 0.01$ for both groups). However, augmentation of reflex vasoconstriction by salt loading was greater in the salt-responsive patients than that in the salt-nonresponsive patients ($P < 0.05$).

**FIGURE 3.** The changes in forearm vascular resistance in response to ice on the forehead during low and high salt diet. High salt diet augmented forearm vascular responses to ice in the salt-responsive as well as in the salt-nonresponsive patients ($P < 0.01$ for both groups). However, augmentation of reflex vasoconstriction by salt loading was greater in the salt-responsive patients than that in the salt-nonresponsive patients ($P < 0.05$).

Forearm vascular response to phentolamine was also greater during the high than during the low salt diet in both salt-responsive ($P < 0.01$) and salt-nonresponsive patients ($P < 0.01$) (Fig. 4). The extent of augmentation of phentolamine-induced vasodilation by salt loading was greater ($P < 0.01$) in salt-responsive patients than in salt-nonresponsive patients (Fig. 4).

**FIGURE 4.** The changes in forearm vascular resistance in response to intravenous phentolamine during high and low salt diet. High salt intake augmented forearm vascular responses to phentolamine in both groups ($P < 0.01$). However, augmentation of phentolamine-induced vasodilation by salt loading was greater in the salt-responsive patients than that in the salt-nonresponsive patients ($P < 0.01$).

Experimental Methods

In this study, we examined maximal vasodilator capacity of the forearm resistance vessels by measuring minimal forearm vascular resistance during peak reactive hyperemia after release of 10 minutes of arterial occlusion (Takeshita and Mark, 1980). We made several assumptions in using this method to evaluate structural vascular changes of the forearm resistance vessels.

The first assumption was that maximal vasodilation of the forearm resistance vessels had been reached during peak reactive hyperemia following 10 minutes of arterial occlusion. However, it was previously shown (Takeshita and Mark, 1980) that increasing metabolic vasodilator stimulus by combining handgrip exercise and 10 minutes of arterial occlusion did not lower minimal vascular resistance more than that following 10 minutes of arterial occlusion alone. Furthermore, an acute elevation of blood pressure produced by intravenous phenylephrine increased peak reactive hyperemia flow after 10 minutes of arterial occlusion, but did not alter minimal forearm vascular resistance (Takeshita et al., 1982). These results suggested that there was maximal vasodilation during...

Discussion

The major finding of this study was that salt loading decreased maximal vasodilator capacity of the forearm resistance vessels in patients with essential hypertension who responded to salt loading with a greater increase in blood pressure. These results suggest that salt loading produced structural vascular changes in the forearm resistance vessels in these hypertensive patients. It is likely that structural vascular changes contributed to the salt-induced increase of forearm vascular resistance in patients who had a greater increase in blood pressure during salt loading.
peak reactive hyperemia after 10 minutes of arterial occlusion.

The second assumption in the method was that the blood pressure measured at the opposite arm would reflect the perfusion pressure to the small arteries in the vasodilated arm. If there was a significant pressure gradient along the large arteries during reactive hyperemia, this assumption would not be true. However, Folkow et al. (1958) found that the large artery pressure gradient during reactive hyperemia was small. Accordingly, we calculated minimal forearm vascular resistance of the vasodilated arm using mean blood pressure measured at the opposite arm.

The third assumption was that the plethysmographic method could be validly applied for the measurements of high blood flow during peak reactive hyperemia. One could consider several possible sources of error in the plethysmographic measurements of blood flow in high flow rates. The first involves venous pressure. The "venous reservoir" of the forearm will be filled rapidly at high flow rates which would result in the substantial increase in venous pressure and lower effective perfusion pressure. However, Folkow (1971) and Conway (1963) found that, even with very high flows, if the veins are emptied or collapsed before the cuff is occluded, as was true in our study, the linear portion of the plethysmographic recording occurs before substantial increases in venous pressure which could interfere with the measurement. The second possible source of error is that effective perfusion pressure might be lowered by a significant pressure gradient along the large arteries at high flow during reactive hyperemia. However, as discussed above, Folkow (1971) showed that this was unlikely. Finally, one could consider the possibility that turbulence might limit peak blood flow. However, this also seems unlikely, since an acute blood pressure decrease caused by ganglionic blockade produced parallel changes in peak blood flow and did not alter minimal vascular resistance (Conway, 1963).

It was shown that the measurement of minimal forearm vascular resistance during peak reactive hyperemia flow following 10 minutes of arterial occlusion was reproducible in the same individuals in three consecutive measurements (Takeshita et al., 1982). It is unlikely that neurohumoral vasoconstrictor stimuli, which might be augmented in hypertensive patients whose blood pressure increases during excess salt intake (Mark et al., 1975; Fujita et al., 1980), limit maximal vasodilation during peak reactive hyperemia. Intraarterial or intravenous administration of phenylephrine, norepinephrine, and angiotensin does not alter minimal vascular resistance during peak reactive hyperemia (Folkow et al., 1958; Conway, 1963; Zelis et al., 1968; Takeshita et al., 1982). Furthermore, it was shown (Takeshita and Mark, 1980) that increased sympathetic vasoconstrictor activity produced by lower body negative pressure does not limit peak reactive hyperemia flow following 10 minutes of arterial occlusion.

Based on these consideration, we interpret the results to suggest that salt loading produced structural vascular changes of the forearm resistance vessels in salt-responsive hypertensive patients but not in salt-nonresponsive hypertensive patients.

Vascular Responses to Salt Loading

In this study, we arbitrarily divided patients with essential hypertension into two groups based on blood pressure response to salt loading and examined the differences in the control of vascular resistance during salt loading between the two groups.

There are two new findings in this study. First, the study demonstrated that salt loading increased forearm vascular resistance in salt-responsive patients but did not alter it in salt-nonresponsive patients. Previous studies indicated that salt-responsive hypertensive patients excreted less sodium in urine and gained more weight during salt loading than did salt-nonresponsive patients (Kawasaki et al., 1978; Fujita et al., 1980). It was thus considered that the greater increase in blood pressure during salt loading in salt-responsive patients might be attributed to a greater sodium retention leading to an increase in cardiac output (Fujita et al., 1980). The results of this study are consistent with these previous reports, but also suggest that—in addition to a greater sodium retention—an altered control of vascular resistance during salt loading contributed to the salt-induced elevation of blood pressure in salt-responsive hypertensive patients.

It should be noted that vascular responses to salt loading in salt-nonresponsive hypertensive patients were different from vascular responses reported in normotensive subjects (Kirkendall et al., 1972). Kirkendall et al. demonstrated that salt loading decreased forearm vascular resistance in normotensive subjects (Kirkendall et al., 1972), whereas, in salt-nonresponsive hypertensive patients in this study, salt loading did not decrease forearm vascular resistance. Thus, it appears that the control of vascular resistance during salt loading was altered even in salt-nonresponsive hypertensive patients, compared to that in normotensive subjects, but the extent of the alteration was less in salt-nonresponsive patients than in salt-responsive patients.

The second and major finding in this study was that salt loading decreased maximal vasodilator capacity of the forearm resistance vessels in salt-responsive hypertensive patients. These results suggest that salt loading produced structural changes in the forearm resistance vessels in salt-responsive hypertensive patients. This consideration, based on decreased maximal vasodilator capacity, was supported by the finding that forearm responses to cold pressor stimuli were augmented during salt loading more in salt-responsive than in salt-nonresponsive hypertensive patients. It was likely that these structural vascular changes contributed to the salt-induced increase of forearm vascular resistance which was observed in salt-responsive hypertensive patients.

We examined maximal vasodilator capacity of the forearm resistance vessels during the 140 mEq salt
diet in only three salt-responsive and two salt-non-responsive patients. Therefore, we can not completely rule out the possibility that the difference in maximal vasodilator capacity during high (345 mEq) and low (70 mEq) salt diet was caused by salt deprivation rather than salt loading. However, blood pressure did not decrease during salt deprivation but increased during salt loading in salt-responsive patients and, more over, in patients in whom the measurements were done at the three levels of salt intake, forehead and to phentolamine tended to be greater than during a low salt diet. Finally, vascular responses to ice on the forehead and to phentolamine tended to be greater during the low salt diet. Thus, it appears that the altered maximal vasodilator capacity was caused by salt loading but not by salt deprivation.

From these physiological observations, we obviously cannot prove or delineate the nature of structural vascular changes. Structural changes might involve the increased thickness of the vessel walls, similar to those reported in spontaneously hypertensive rats (Limas et al., 1980), or the increase in sodium or water in the vessels (Tobian and Binion, 1952; Folkow, 1971).

By inbreeding, Dahl et al. developed two strains of rats, salt sensitive and salt resistant, which have markedly different genetic propensities for development of hypertension during excess salt intake (Dahl et al., 1967). It should be noted that this study does not imply that there are two distinct groups of patients with essential hypertension, salt sensitive and salt resistant, as is true in the case of the Dahl strain of rats. In this study, two groups of hypertensive patients were arbitrarily divided, based on the extent of blood pressure rise on salt loading, to see whether there was a difference between them with regard to maximal vasodilator capacity during salt loading. Besides the difference in vascular responses to salt loading, there were other differences between the two hypertensive groups. Salt-responsive patients had higher blood pressure response to ice than did salt-nonresponsive patients. Another difference was that blood pressure in salt-responsive patients was unchanged after admission on low salt diet but increased on high salt diet, whereas, in salt-nonresponsive patients, blood pressure fell after admission on low salt diet and did not increase on high salt diet. Salt-responsive patients excreted less sodium in urine and gained more weight during salt loading than did salt-nonresponsive patients. Plasma renin activity was lower in salt-responsive patients during low salt diet. These results might suggest that salt-responsive patients retained more sodium during a high as well as a low salt diet. Finally, vascular responses to ice on the forehead and to phentolamine tended to be greater in salt-responsive patients than in salt-nonresponsive patients during low salt diet, even though maximal vasodilator capacity was not different between the two groups during low salt diet. These results may suggest that the integrity of adrenergic innervation or vascular responsiveness to adrenergic stimuli might be different between the two groups during low salt diet. The importance of each of these differences as a factor that affects vascular responses to salt loading should be clarified in future studies.

Since blood pressure in salt-responsive patients on a low salt diet was higher than in salt-nonresponsive patients on the same diet, one may consider the possibility that the difference in vascular response to salt loading might be due to the difference in the severity of hypertension. To examine this possibility, we compared the results between the subgroups of patients of each group who were selected so that the average mean blood pressures in the two subgroups were not different. The two subgroups had similar blood pressures, 103 ± 2 mm Hg for the salt-responsive group (n = 5) and 102 ± 2 mm Hg for the salt-nonresponsive group (n = 7) (P < 0.05). In the subgroup of salt-nonresponsive patients, maximal vasodilator capacity of the forearm resistance vessels did not change during salt loading (minimal forearm vascular resistance 2.0 ± 0.1 units on low salt diet and 2.0 ± 0.1 units on high salt diet, P > 0.05), whereas, in the subgroup of salt-responsive patients, maximal vasodilator capacity decreased during salt loading (minimal forearm vascular resistance 1.8 ± 0.2 units on low salt diet and 2.5 ± 0.2 units on high salt diet, P < 0.05). These results might suggest that the difference in vascular response to salt loading between the two groups of hypertensive patients was not totally due to the differences in blood pressure. However, this possibility should be examined in the larger group of patients.

Previous studies suggested that augmented neurogenic mechanisms importantly contribute to salt-induced vasoconstriction in the salt-responsive humans and animals with genetic hypertension (Mark et al., 1975; Takeshita and Mark, 1978; Takeshita et al., 1979; Fujita et al., 1980). Our results are not inconsistent with this view. It is possible that augmented neural activity, in addition to the structural vascular changes, might have contributed to the greater responses to ice or phentolamine during high salt in salt-responsive patients. Forearm vascular responses to ice or phentolamine were greater during the high salt than during the low salt diet in salt-nonresponsive patients in whom basal vasodilator capacity was not altered by salt loading.

During the low salt diet, two salt-nonresponsive patients had forearm vasodilation in response to ice on the forehead, and, in one salt-nonresponsive patient, phentolamine did not dilate forearm vessels. The reasons for the unexpected responses in these patients were not clear. However, these patients were more than 60 years old and had mild orthostatic hypotension during low salt diet. These findings might be related to reduced reflex adrenergic vasoconstriction which has been observed during low salt intake (Rocchini et al., 1977) and to sympathetic cholinergic vasodilation which was noted in patients with orthostatic hypotension in response to ice on the forehead (Abboud et al., 1976).

In summary, the results of this study were consistent with the view that salt loading produced structural vascular changes in the forearm resistance ves-
sels in patients with essential hypertension who responded to salt loading with a greater rise of blood pressure. It is considered that structural vascular changes contributed to the salt-induced vasoconstriction and thus to the salt-induced elevation of blood pressure in these patients.

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