HEMODYNAMIC RESPONSE TO DIETARY SODIUM LOADING IN ESSENTIAL HYPERTENSION STUDIED WITH DOPPLER ECHOCARDIOGRAPHY

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The cardiac response to dietary salt loading was assessed by Doppler echocardiography during various sodium intakes (52—345 mEq per day) in 30 patients with essential hypertension. The mitral flow velocity integral in the rapid filling phase (IntR) and the atrial contraction phase (IntA) was measured from the transmitral flow pattern, and the sum of IntR and IntA (IntR + IntA), the ratio of IntA to IntR (IntA/IntR), cardiac output (CO) and total peripheral resistance (TPR) were calculated. With salt loading, the mitral flow pattern remained almost unchanged in the nonsalt-sensitive (NSS) patients. Fourteen of the 19 salt-sensitive (SS) patients showed significant increases in IntR + IntA and CO with salt loading (IntR + IntA, from 13.9 ± 2.8 to 17.9 ± 3.6 cm, p < 0.01; CO, from 6021 ± 2130 to 8305 ± 1699 ml/min, p < 0.01), and were termed “salt-sensitive CO-dependent” (SS [COdep]), suggesting that the apparent pressor response to sodium loading was mediated by an increased CO. In the remaining five SS patients termed “salt-sensitive CO-independent” (SS [COindep]), IntA/IntR increased significantly with sodium repletion (from 0.66 ± 0.23 to 0.90 ± 0.31, p < 0.01), without a significant change in IntR + IntA. Increments in IntA/IntR observed in the SS [COindep] patients were considered to be due to an elevation of total peripheral resistance (TPR), since changes in IntA/IntR were significantly correlated with those in TPR in all subjects (r = 0.617, p < 0.01).

EPIDEMIOLOGICAL and experimental studies have demonstrated a relationship between dietary sodium intake and the incidence of hypertension!–3 Although almost everyone ingests an excess of sodium beyond the threshold needed to induce hypertension, the majority of the population remains free of hypertension suggesting that some individuals are susceptible to sodium intake while others are resistant. Kawasaki et al4 identified a subgroup of patients with essential hypertension displaying an increase in blood pressure during sodium loading (“salt-sensitive”). It has been reported that sodium repletion induces various hemodynamic changes in man and animals5–8 Despite these observations, the mechanisms responsible for this varying behavior of patients with essential hypertension in response to sodium intake are not fully understood.

Key words:
Hypertension
Sodium
Cardiac output
Total peripheral resistance
Doppler echocardiography

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The purpose of this study was to analyze the transmirtal flow pattern using pulsed Doppler echocardiography in subjects with essential hypertension, and to evaluate the effects of high and low sodium intake on arterial pressure, cardiac output (CO) and total peripheral resistance (TPR).

METHODS

The subjects were 30 patients with essential hypertension in WHO Stage I or II (16 men, 14 women) aged 34 to 75 years (53.0 ± 9.3 years). All subjects were admitted to the First Department of Internal Medicine, Hiroshima University School of Medicine for interviews, physical examinations and laboratory studies. Patients were considered to have hypertension if, during three subsequent visits to the outpatient clinic, their blood pressure was found to be equal to or higher than 160/95 mmHg. All subjects showed normal sinus rhythm. In none of the patients was a specific cause of hypertension found. Details in the study were explained and informed consent was obtained from all subjects. The administration of all antihypertensive drugs was discontinued at least 4 weeks prior to the study.

Patients were studied for 1 week on a daily diet containing 10g of salt (172 mEq of

sodium, “average-sodium”), then for 1 week on a diet with 3 g of salt (52 mEq of sodium, “low-sodium”) and finally for 1 week on a diet with 20 g of salt (345 mEq of sodium, “high-sodium”). Blood pressure and hemodynamic indices were measured on the fifth day of the low-sodium and high-sodium regimens. After 30 min rest in the supine position, blood pressure was measured in triplicate by sphygmomanometer before, during and after echocardiographic studies. Mean blood pressure (MBP) was calculated as the sum of diastolic blood pressure and one-third of pulse pressure. Patients whose average MBP value on day 5 of the high-sodium regimen exceeded by 5% or more that of the low-sodium regimen on day 5 were defined as “salt-sensitive” (SS), those whose average MBP did not change or increased less than 5%, were defined as “nonsalt-sensitive” (NSS).

The hemodynamic studies included pulsed Doppler echocardiography from which mitral velocity integrals, CO and TPR were determined (Fig. 1). Echocardiographic studies were performed with patients in a supine position, Echo images were obtained with a wideangle phased array echograph, Toshiba Sonolayergraph SSH40A and SSH65A, incorporating a directionl pulsed
### TABLE II DIFFERENCES IN CENTRAL HEMODYNAMICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonsalt-sensitive</th>
<th>Salt-sensitive CO-dependent</th>
<th>Salt-sensitive CO-independent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low sodium</td>
<td>High sodium</td>
<td>Low sodium</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>113.9±13.2</td>
<td>114.4±12.7</td>
<td>107.2±12.6</td>
</tr>
<tr>
<td>Difference (mmHg)*</td>
<td>0.5±2.3</td>
<td>13.8±6.8</td>
<td>13.6±5.5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65.4±15.1</td>
<td>65.7±16.4</td>
<td>67.5±9.9</td>
</tr>
<tr>
<td>Difference (beats/min)*</td>
<td>0.3±4.9</td>
<td>-2.8±9.0</td>
<td>-3.6±3.9</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>5757±1377</td>
<td>6149±1629</td>
<td>6021±2130</td>
</tr>
<tr>
<td>Difference (ml/min)*</td>
<td>392±903</td>
<td>2284±1529†</td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance (mmHg/l/min)</td>
<td>20.7±4.2</td>
<td>19.6±4.6</td>
<td>20.5±8.5</td>
</tr>
<tr>
<td>Difference (mmHg/l/min)*</td>
<td>-1.0±3.2</td>
<td>-5.37±6.57†</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as means±SD. Low sodium=the 5th day of the low sodium diet. High sodium=the 5th day of the high sodium diet.

*Changes from low sodium to high sodium diets.

†p<0.05, ‡p<0.01, statistical significance of differences between low and high sodium diets.

### TABLE III DIFFERENCES BETWEEN MEASUREMENTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonsalt-sensitive</th>
<th>Salt-sensitive CO-dependent</th>
<th>Salt-sensitive CO-independent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low sodium</td>
<td>High sodium</td>
<td>Low sodium</td>
</tr>
<tr>
<td>IntR+IntA (cm)</td>
<td>13.6±3.1</td>
<td>14.1±3.0</td>
<td>13.9±2.8</td>
</tr>
<tr>
<td>Difference (cm)*</td>
<td>0.5±0.9</td>
<td>4.0±1.8†</td>
<td>-0.13±0.22‡</td>
</tr>
<tr>
<td>IntA/IntR</td>
<td>0.70±0.20</td>
<td>0.70±0.19</td>
<td>0.78±0.32</td>
</tr>
<tr>
<td>Difference*</td>
<td>0.00±0.06</td>
<td></td>
<td>-0.13±0.22‡</td>
</tr>
<tr>
<td>Plasma norepinephrine (ng/ml)</td>
<td>0.213±0.155</td>
<td>0.115±0.053</td>
<td>0.268±0.111</td>
</tr>
<tr>
<td>Difference (ng/ml)*</td>
<td>-0.099±0.119†</td>
<td>-0.020±0.164</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as means±SD. Low sodium=the 5th day of the low sodium diet. High sodium=the 5th day of the high sodium diet.

*Changes from low sodium to high sodium diets.

†p<0.05, ‡p<0.01, statistical significance of differences between low and high sodium diets.
Doppler flowmeter, Toshiba SDS21A. The ultrasound frequency of the Doppler flowmeter was 2.4 MHz and the pulse repetition rate was 4 or 6 kHz. The size of the sample volume was about 4 mm (width) x 2 mm (depth). The Doppler signals were displayed simultaneously with the electrocardiogram, phonocardiogram and M-mode echocardiogram using a strip chart recorder (Toshiba LSR20A) at a paper speed of 50 mm/sec. Flow velocity components towards and away from the transducer were displayed above and below the baseline, respectively. The transducer was placed at the apical impulse and the apical long-axis view was imaged. The Doppler sample volume was placed in the center of the mitral ring, corresponding to the D point on the derived M-mode mitral valve echogram. The mitral flow velocity integrals (measured by planimetering mitral flow velocity curve) were designated as the integral of the rapid filling phase (IntR), and the integral of the atrial contraction phase (IntA). The sum of IntR and IntA (IntR+IntA) and the ratio of IntA to IntR (IntA/IntR) were calculated. The diameter of the mitral valve annulus was measured from the parasternal long-axis view of the left ventricle at the time of the peak rapid filling flow velocity, and the cross-sectional area of the mitral valve annulus was calculated, assuming it to be circular in shape in short axis. Doppler-derived CO was determined using the following formula:

\[ CO(\text{ml/min}) = \text{IntR + IntA (cm)} \times \pi \times (D(cm)/2)^2 \times \text{heart rate (beats/min)} \]

where D means the anterior-posterior diameter of the mitral valve annulus on the two-dimensional echocardiogram in mid-diastole.

For preliminary study, this method was used in 29 adult patients (55.3 ± 10.2 years, 18 men 11 women) who were studied to determine the clinical value of the mitral valve method. Admission diagnoses included myocardial infarction in 16 patients and angina pectoris in 8 patients. Five patients had undergone coronary artery bypass grafting. None had mitral insufficiency or mitral valve disease. Mitral valve flow measurements by Doppler were compared to standard thermodilution COs performed with a thermodilution computer system (American Edwards Laboratories, COC-9520-A) as an average of three injections.

TPR was calculated from the following formula using simultaneous MBP and CO.
TPR[mmHg/l/min] = MBP[mmHg]/CO[ml/min]×10³

On the seventh day of the average-sodium diet, the determination of plasma renin activity (PRA) was performed after the administration of furosemide 40 mg intravenously during which time the patients remained upright. PRA was measured by radioimmunoassay. Plasma norepinephrine (NE) was determined on the seventh day of the low-sodium and high-sodium diets. Plasma NE was measured by an electrochemical method using high performance liquid chromatography.

STATISTICS

Data are expressed as mean ± standard deviation, and differences were evaluated by the nonparametric test of the Wilcoxon matched-pairs signed-rank test, Wilcoxon U test, or one-way analysis of variance as appropriate. \( p < 0.05 \) was considered to be statistically significant.

RESULTS

(1) Relationship between CO determined by Doppler and standard thermodilution CO

In the preliminary study of 29 adult patients, the correlation coefficient between Doppler and thermodilution COs was 0.89 (thermodilution CO[1/min] = 1.12 Doppler CO[1/min] − 0.06, Fig. 2).

(2) Subclassification of the patients

Nineteen patients fell into the SS group and 11 fell into the NSS group by our criteria.

There was a significant and direct, but weak, correlation between the per cent change in MBP and the change in IntR + IntA (\( \Delta [\text{IntR} + \text{IntA}] = 0.156\% \Delta \text{MBP} + 0.787, r = 0.567, p < 0.01 \)) observed during the change from low to high sodium intake in all subjects (Fig. 3). Neither the level of MBP during low sodium intake nor the per cent change in MBP from low to high salt intake correlated with the level of IntR + IntA during low salt intake. Although there was a weak correlation between the per cent change in MBP from low to high salt intake and the level of IntR + IntA during high sodium diet (\( r = 0.389, p < 0.05 \)), there was no significant correlation between the levels.
of MBP and IntR + IntA during high sodium intake. There was no significant change in IntR + IntA with the salt loads in the NSS patients (from 13.6 ± 3.1 to 14.1 ± 3.0 cm). In the SS patients the change in IntR + IntA varied considerably; some showed little increase in IntR + IntA when their MBP rose, while the others showed increases in IntR + IntA in proportion to their elevated MBP. According to the level of the mean ± 2SD (standard deviation) of the change in IntR + IntA in the NSS patients, 19 SS patients were divided into two groups— one “salt-sensitive CO-dependent” group (SS [COdep]) in which sodium loading increased IntR + IntA more than the level, and the other “salt-sensitive CO-independent group” (SS [COindep]) in which it did not. Table I summarizes clinical findings of patients on admission. There was no significant difference in age among the three groups. The summary of the data on MBP, heart rate, IntR + IntA, IntA/IntR, CO, TPR and plasma NE in all patients is given in Tables II and III. There was no significant change in heart rate with salt loads in three groups.

(3) Changes in Int R, Int A in each group
There was no significant difference in IntR + IntA levels among the three groups during
low sodium diet. During high salt intake, \( \text{IntR} + \text{IntA} \) levels increased significantly in the SS [COdep] patients (from 13.9±2.8 to 17.9±3.6 cm, \( p < 0.01 \)), but they did not in the SS [COindep] patients (from 14.2±0.9 to 14.6±1.0 cm) (Fig. 4). The levels of \( \text{IntR} + \text{IntA} \) were significantly higher in the SS [COdep] patients than in the NSS subjects during high salt intake (\( p < 0.05 \)). There was, however, no difference in \( \text{IntR} + \text{IntA} \) levels between the SS [COdep] and SS [COindep] patients during sodium repletion.

\( \text{IntA/IntR} \) did not change in the NSS patients (from 0.70±0.20 to 0.70±0.19), decreased significantly in the SS [COdep] patients (from 0.78±0.32 to 0.65±0.18, \( p < 0.05 \)) and increased significantly in the SS [COindep] patients (from 0.66±0.23 to 0.90±0.31, \( p < 0.01 \)), with sodium repletion (Fig. 5). There was no significant difference in \( \text{IntA/IntR} \) levels among the three groups before and after sodium repletion.

The change in \( \text{IntR} + \text{IntA} \) for each patient is plotted against the change in \( \text{IntA/IntR} \) for that patient with sodium loading in Fig. 6. The NSS patients near the zero point, indicating that there was no significant change in \( \text{IntA} + \text{IntR} \) and \( \text{IntA/IntR} \) with salt repletion. The SS [COdep] patients fell into a separate group from the SS [COindep] subjects. In the SS [COdep] subjects, \( \text{IntR} + \text{IntA} \)
IntA levels increased significantly, while IntA/IntR decreased significantly with salt loading. There were significant increments in IntA/IntR in the SS [COindep] individuals without significant change in IntR + IntA.

Typical changes in the mitral flow pattern in two types of SS group are shown in Fig. 7.

(4) Changes in CO and TPR in each group
There was no significant difference in CO levels among the three groups before sodium repletion. The levels of CO were significantly higher in the SS [COdep] patients than in the NSS subjects and in the SS [COindep] subjects during high salt intake (both, p < 0.01). When comparing the values of CO between low sodium and high sodium diets, we found that there were significant increments in the SS [COdep] subjects (from 6021 ± 2130 to 8305 ± 1699 ml/min, p < 0.01) but not in the NSS (from 5757 ± 1377 to 6149 ± 1629 ml/min) and SS [COindep] subjects (from 5501 ± 1016 to 5293 ± 613 ml/min) (Fig. 8). Increments in CO from low to high salt intake were significantly greater in the SS [COdep] patients than those in the NSS subjects and in the SS [COindep] subjects (both, p < 0.01). Since there were no significant changes in heart rate and the diameter of mitral annulus with salt loading in three groups, it is supposed that the change in CO would be proportional to that in IntR + IntA with sodium repletion.

There were no difference in TPR levels among the three groups before salt repletion. The levels of TPR were significantly lower in the SS [COdep] patients than in the NSS subjects and in the SS [COdep] subjects (both, p < 0.01). There was no significant change in TPR between salt loads in the NSS group (from 20.7 ± 4.2 to 19.6 ± 4.6 mmHg/l/min). TPR fell from 20.5 ± 8.5 to 15.1 ± 3.0 mmHg/min in the SS [COdep] and rose from 18.8 ± 2.2 to 21.9 ± 2.3 mmHg/min in the SS [COindep] subjects (both, p < 0.05) (Fig. 9). Changes in TPR from low to high sodium intake were significantly higher in the SS [COindep] patients than in the NSS patients or in the SS [COdep] patients (both, p < 0.05).

When data from three groups were considered together, there was a significant positive correlation between the change in TPR and IntA/IntR with the salt loads (∆IntA/IntR = 0.218 ∆ TPR + 0.0266, r = 0.617, p < 0.01) (Fig. 10). Thus the increase in IntA/IntR in the SS [COindep] group was supposed to reflect the elevated TPR.

(5) Endocrinological data
During sodium depletion, plasma NE levels did not vary between the three groups. With salt loading, plasma NE levels decreased significantly in the NSS patients (from 0.213 ± 0.155 to 0.115 ± 0.53 ng/ml, p < 0.05), but did not fall in the SS [COdep] (from 0.268 ± 0.111 to 0.248 ± 0.183 ng/ml) and SS [COindep] individuals (from 0.226 ± 0.172 to 0.285 ± 0.128 ng/ml).

With furosemide on the seventh day of the average-sodium diet, PRA was significantly lower (p < 0.05) in the SS[COdep] patients (2.55 ± 2.17 ng/min/h) than in the NSS patients (4.53 ± 1.89 ng/ml/hr). PRA was not different between the SS [COdep] and SS [COindep] subjects (2.60 ± 1.08 ng/min/h) (Table IV).

DISCUSSION
Since the two factors that determine blood pressure are CO and TPR, the pressor effect of salt repletion is expected to be the result of an increase in either CO or TPR. There have been contradictory reports on the influences of sodium intake in central hemodynamics. Fujita et al. suggested that an increase in CO may contribute to the rise in MBP upon salt repletion. Sullivan et al. suggest that the basis of MBP elevation during salt repletion in the SS subjects may be a failure to lower TPR adequately when CO rises.

We have observed that NSS patients do not show a significant change in either CO or TPR with salt loading, and that SS patients show a heterogenous response to sodium repletion, some being accompanied with an increase in CO and other with a rise in TPR. It has been reported that sympathetic drive may be readily lowered by salt loading in NSS patients, whereas salt repletion could enhance sympathetic nervous activity in SS subjects. Our data on plasma NE supports these previous studies. However, we found no factor which could account for the differences between the SS [COdep] and SS [COindep] subjects, because differences in plasma NE and PRA between the two SS
groups were not significant before or after salt repletion.

In our study, recording transmural flow patterns offers considerable advantage in analyzing the characteristic features of the NSS and SS patients. While the mitral flow velocity pattern remained almost unchanged in the NSS patients, the SS [COdep] subjects were characterized by an increase in IntR + IntA, and the SS [COindep] subjects were characterized by an increased IntA/IntR. It has been known that an acute increase in afterload may disturb diastolic rapid filling of the left ventricle. Since we have observed that there was a significant positive correlation between changes in TPR and those in IntA/IntR, a chronic increase in TPR with sodium loading may impair diastolic rapid filling of the left ventricle in SS [COindep] patients, resulting in an increase in IntA/IntR.

It has been reported that CO calculated by measuring the mitral flow velocity using Doppler echocardiography correlates well with other methods of CO measurements. Our preliminary observations also showed a high correlation between mitral valve flow measurement by Doppler and standard thermodilution CO. This Doppler technique is, therefore, well suited for assessing CO responses to any interventions.

In conclusion, we have observed that the response to sodium repletion is heterogenous and that the measurement of mitral flow parameters such as IntR + IntA and IntA/IntR may provide a useful approach in distinguishing SS [COdep] patients from SS [COindep] subjects.

REFERENCES
