Dietary Salt Intake
A Determinant of Cardiac Involvement in Essential Hypertension

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Because a given increase in afterload does not consistently produce the same degree of left ventricular hypertrophy, we evaluated several clinical, hemodynamic, and endocrine factors that are prone to modify the adaptation of left ventricular structure in patients with mild essential hypertension (World Health Organization stages I or II). Dietary salt intake assessed by sodium excretion over 24 hours was a powerful determinant of posterior wall thickness \( (r=0.64, \ p<0.001) \), relative wall thickness \( (r=0.67, \ p<0.001) \), and left ventricular mass \( (r=0.37, \ p<0.05) \). In contrast, diastolic pressure, body mass index, hematocrit, and epinephrine were found to be weaker determinants of left ventricular structure \( (r=0.31-0.40, \ p<0.05) \). A stepwise multiple regression analysis revealed that sodium excretion was the strongest predictor for posterior wall thickness \( (p<0.02) \) and relative wall thickness \( (p<0.05) \) independent of the other examined variables. These results identify dietary salt intake as a strong determinant of cardiac structural adaptation to a persistent increase in arterial pressure. Consequently, a high salt intake might aggravate and, conversely, dietary salt restriction might prevent (or at least mitigate) the development of left ventricular hypertrophy in patients with essential hypertension. *(Circulation 1988;78:951–956)*

Sodium homeostasis profoundly influences the cardiovascular system in normotensive and hypertensive subjects.\(^1\)\(^-\)\(^3\) High salt intake in normotensive individuals produces a rise in cardiac output by increasing preload of the left ventricle but does not change arterial pressure because total peripheral resistance seems to fall proportionally.\(^4\) In contrast, in patients with borderline hypertension, high dietary salt intake leads to an increase in arterial pressure because of a disproportionate rise in cardiac output and an inadequate fall in total peripheral resistance, thereby increasing the pressure load on the left ventricle.\(^5\) However, not all hypertensive patients appear to be equally sensitive to changes in dietary salt intake.\(^6\) Approximately one half of the hypertensive population show an inappropriate modulation of the renin-angiotensin-aldosterone cascade during salt loading.\(^7\)\(^-\)\(^10\) Sodium homeostasis is linked not only to the renin-angiotensin-aldosterone system but to the sympathetic adrenergic system as well.

High sodium intake has been reported to cause an exaggerated pressor response to exogenous norepinephrine in normotensive subjects.\(^11\)\(^,\)\(^12\) Although the increase in afterload caused by arterial hypertension has been regarded to be the major culprit for the development of left ventricular hypertrophy, both the adrenergic and renin-angiotensin-aldosterone systems have been implicated in modifying this structural cardiac adaptation in essential hypertension.\(^13\)\(^-\)\(^20\) Other parameters such as being overweight, race, sex, age, and blood viscosity further influence cardiac adaptation in arterial hypertension.\(^17\)\(^,\)\(^21\)\(^-\)\(^26\) Because sodium homeostasis interferes with these determinants of myocardial hypertrophy, dietary salt intake might play a pathogenetic role in the process of left ventricular hypertrophy in essential hypertension. The present study was therefore designed to, first, elucidate whether dietary salt intake affected the process of structural adaptation of the left ventricle at all, and, second, analyze whether sodium intake influences the development of left ventricular hypertrophy independently from other determinants.

**Subjects and Methods**

**Study Population**

A total of 42 patients with essential hypertension (World Health Organization [WHO] stages I or II)
were enrolled in this protocol who consecutively consulted our outpatient clinic and in whom an echocardiographic and hemodynamic evaluation could be performed. Patients were considered to have established hypertension if their diastolic pressure was consistently more than 90 mm Hg (Korotkoff phase V) measured after 5 minutes of rest in our outpatient clinic (with an appropriate cuff in obese patients). Secondary causes of arterial hypertension and WHO stages III and IV were ruled out by routine clinical and laboratory examinations, as previously outlined.27 All patients had either never been treated in the past or, if they had been (mean duration of therapy 5.4 ± 2.3 years), did not receive antihypertensive medication for at least 4 weeks before the examination. The patients did not follow any guidelines with regard to salt intake. Clinical, echocardiographic, hemodynamic, and endocrine data of our study population are listed in Table 1. Besides weight, body mass index (wt/ht\(^2\)) was chosen as an index for being overweight.28 Diastolic pressure dropped to less than 90 mm Hg in some patients when measured in our laboratory under complete resting conditions. The protocol for the study was approved by the Institutional Clinical Investigation Committee, and informed consent was obtained.

**Hemodynamic Measurements**

As previously reported, a hemodynamic evaluation was done simultaneously with the echocardiographic study.27 Briefly, cardiac output was measured in triplicate with indocyanine green, and intra-arterial pressure was obtained by catheter with its tip in the subclavian artery or aortic arch. Mean arterial pressure was obtained by electrical integration. Stroke volume and total peripheral resistance were calculated by standard formulas. Plasma volume was determined during the hemodynamic study by injecting \(^{125}\)I-labeled serum albumin and measuring the decline of the radioactivity after 15 and 30 minutes of equilibration. Hematocrit was measured routinely and total blood volume was calculated (plasma volume/100 minus hematocrit).

About 1 hour after patients were lying down and the catheters had been inserted, blood was drawn into ice-cooled tubes and stored at −21°C. Circulating norepinephrine, epinephrine, and dopamine were measured by radioenzymatic assay.29 Plasma renin activity was measured by radioimmunoassay (generated angiotensin I after 5 hours of incubation).27,30 In addition, we measured angiotensin I at point zero (that was synthesized before starting the incubation period).

The day before the baseline examination, the patients were told to collect urine over 24 hours. On the day of the examination, creatinine and sodium were determined in the serum and in the 24-hour urine. Five urine samples were excluded because either the urine volume was less than 600 ml and/or excreted urine creatinine was below a value that should have been excreted according to the body weight.31 In the remaining 37 patients, sodium excretion over 24 hours was taken as an index for dietary salt intake.32 Sodium excretion ranged from 37 to 356 meq/day. Glomerular filtration rate was assessed by creatinine clearance.33,34

**Echocardiography**

Standard methods of M-mode echocardiographic study were conducted as previously reported with an ultrasonoscope (Ecoline 28, Smith-Kline, Sunnyvale, California) interfaced with a strip chart recorder (Honeywell, Denver, Colorado) and a probe measuring 1.27 cm in diameter.35,36 Ultrasonic admission characteristics were as follows: frequency, 1,000/sec; wavelengths, 2.25 mHz; and focal length, 10 cm. Echocardiograms were recorded in the third or fourth left interspace with the patient in half left-sided position. All traced echocardiograms were read by two trained physicians.

Septal and posterior wall thicknesses were measured according to the standard measurement convention of the American Society of Echocardiography including the thickness of the endocardial

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**Table 1. Clinical, Hemodynamic, Echocardiographic, and Endocrine Characteristics of All Patients**

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.2 ± 10.4</td>
</tr>
<tr>
<td>Man:woman</td>
<td>32:10</td>
</tr>
<tr>
<td>Race (white:black)</td>
<td>26:16</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 ± 15</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>28.7 ± 5.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42 ± 4.1</td>
</tr>
<tr>
<td>Sodium excretion (meq/24 hr)</td>
<td>136 ± 69</td>
</tr>
<tr>
<td>Casual blood pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>153 ± 14</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>100 ± 6</td>
</tr>
</tbody>
</table>

**Echocardiographic data**

| Septal thickness (cm)                       | 1.21 ± 0.19   |
| Posterior wall thickness (cm)               | 1.02 ± 0.13   |
| Septal:posterior wall ratio                 | 1.21 ± 0.21   |
| Relative wall thickness                     | 0.44 ± 0.08   |
| Left ventricular mass (g)                   | 218 ± 35      |
| Left ventricular mass index (g/m\(^2\))     | 110 ± 32      |
| End-diastolic diameter (cm)                 | 4.73 ± 0.69   |
| End-systolic diameter (cm)                  | 2.97 ± 0.55   |

**Systemic hemodynamics**

| Systolic pressure (mm Hg)                   | 154 ± 21      |
| Mean arterial pressure (mm Hg)              | 109 ± 12      |
| Diastolic pressure (mm Hg)                  | 86 ± 10       |
| Heart rate (beats/min)                      | 68 ± 9        |
| Cardiac output (l/min)                      | 5.80 ± 1.2    |
| Stroke volume (ml/min)                      | 85 ± 15       |
| Total peripheral resistance (U)             | 19 ± 4.1      |
| Plasma volume (ml)                          | 3,135 ± 634   |
| Total blood volume (ml)                     | 5,097 ± 1,184 |

**Endocrine parameters**

| Norepinephrine (pg/ml)                      | 223 ± 87      |
| Epinephrine (pg/ml)                         | 23 ± 14       |
| Dopamine (pg/ml)                            | 13 ± 8        |
| Plasma renin activity (ng/ml/hr)            | 2.1 ± 1.8     |
| Angiotensin I (ng/ml)                       | 1.12 ± 0.6    |
| Aldosterone (ng/dl)                         | 10.4 ± 8.5    |
TABLE 2. Determinants for Left Ventricular Hypertrophy (Linear Regression Coefficients)

<table>
<thead>
<tr>
<th>Sodium excretion</th>
<th>0.38*</th>
<th>0.64§</th>
<th>0.67§</th>
<th>0.37†*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>. .</td>
<td>0.33*</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>. .</td>
<td>0.31*</td>
<td>0.24§</td>
<td>. .</td>
</tr>
<tr>
<td>Body mass index</td>
<td>. .</td>
<td>0.38§</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>. .</td>
<td>0.35*</td>
<td>0.40§</td>
<td>. .</td>
</tr>
</tbody>
</table>

*p<0.05; †p<0.001; ‡p<0.10; §p<0.01; all other correlations were not significant.

Echocardiographic variables.36,37 Patients with a septal:posterior wall thickness ratio of more than 1.3 were considered to have isolated septal hypertrophy. Relative wall thickness, regarded as a valid parameter for concentric hypertrophy of the left ventricle, was determined by dividing posterior wall thickness by half of the end-diastolic diameter.38,39 Left ventricular mass was calculated according to the formula of Bennett and Evans.40,41 Septal wall thickness, posterior wall thickness, and relative wall thickness, as well as left ventricular mass, were taken as indexes for the degree of left ventricular hypertrophy.

Statistics
Linear correlation coefficients (Pearson) were calculated among the four indexes of left ventricular hypertrophy and all other evaluated variables. To weigh or quantify the influence of various determinants for left ventricular hypertrophy, a stepwise multiple regression analysis (Statistical Package of Social Sciences) was performed with 37 patients who all had a complete evaluation.42 Unless otherwise specified, all data are expressed as mean ± SD.

Results
The strongest determinant for posterior wall and relative wall thickness was sodium excretion (Table 2): the higher the sodium excretion, the thicker was the posterior wall and the greater the relative wall thickness (Figures 1 and 2). Because sodium excretion did not correlate with end-diastolic volume (which predicted 73% of the variance of left ventricular mass in our sample), it is not surprising that dietary salt intake correlated only modestly with left ventricular mass (Figure 3). Sodium excretion correlated modestly well with septal wall thickness in the whole population. However, when 11 patients with isolated septal hypertrophy (representing a distinct entity of cardiac hypertrophy) were excluded in a subsequent analysis, the correlation coefficient improved from 0.38 to 0.78 (p<0.001), indicating the same close relation for the septal wall thickening with sodium excretion as we found for the posterior wall.

Of all the examined endocrine parameters, only plasma epinephrine disclosed a positive weak relation to the posterior wall thickness (Table 2). Plasma renin activity, angiotensin I, and aldosterone did not reveal any direct influence on the degree of left ventricular hypertrophy. Norepinephrine or dopamine levels measured in the central venous blood were also not linked to any of the echocardiographic variables.

Low-grade clinical determinants for posterior wall thickness and relative wall thickness were diastolic pressure, body mass index, and hematocrit (Table 2). None of the systemic hemodynamic parameters (stroke volume, cardiac output, and total peripheral resistance) correlated with any of the indexes for left ventricular hypertrophy in our sample; neither did age, sex, race, total blood volume, or plasma volume.

Sodium excretion was related to diastolic pressure (r= +0.48, p<0.01), plasma renin activity (r= -0.33, p<0.05), and hematocrit (r=0.32, p<0.05) but not with body mass index. Subsequently, stepwise multiple regression analyses were performed to evaluate the impact of sodium excretion on myocardial hypertrophy. Sodium excretion was defined as the most powerful determinant of wall thickness (standardized regression coefficient β=0.495, p<0.02) and of relative wall thickness (standardized regression coefficient β=0.379, p<0.05) independent of the other variables. More than half of the variance in the posterior wall thickness could be predicted when 24-hour urinary sodium excretion, diastolic pressure, body mass index, and hematocrit were taken into account (r²= 56.6).

Discussion
Among all evaluated clinical, hemodynamic, and endocrine parameters, dietary sodium intake as evaluated by measuring sodium excretion evolved as the best predictor of the degree of left ventricular hypertrophy in patients with essential hypertension. The
relation between sodium excretion and left ventricular hypertrophy remained significant even when its interrelation with arterial pressure, being overweight, hematocrit, and endocrine factors was taken into account. Arterial pressure, being overweight, and hematocrit evolved as low-grade determinants for left ventricular structural adaptation, which is in accordance with previous studies. Because hematocrit can be regarded as a crude measure of blood viscosity, the loose association of hematocrit with posterior wall thickness corroborates findings of Devereux et al showing a close correlation between blood viscosity and left ventricular hypertrophy in systemic hypertension. Experimental studies corroborate our findings that dietary sodium intake modulates cardiac hypertrophy independent of the pressure overload imposed on the left ventricle in hypertensive patients. In renal hypertensive rats, dietary sodium restriction led to a significant reduction of relative heart weight compared with rats on a normal diet, although hypertension was not reversed. Furthermore, in these animals, sodium restriction restored tissue catecholamine content and the myosin isozymic distribution pattern to normal values of the nonhypertrophied heart.

What are the pathogenetic mechanisms linking dietary sodium intake to left ventricular hypertrophy in essential hypertension? Any close correlation between two parameters indicates that either one influences the other (and vice versa) or that both are regulated by a common underlying factor. In this context, three hypotheses come to mind: 1) The reactivity of the sympathetic nervous system that has been shown to be a determinant of left ventricular hypertrophy increases in parallel with dietary salt intake. Exogenous catecholamines have been documented to induce myocardial hypertrophy, even in supressor doses. Conversely, centrally acting antiaergeric agents as well as β-adrenoreceptor blockers produce a regression of left ventricular mass even when arterial pressure is not completely controlled. Because the activity of the sympathetic nervous system is not very accurately reflected by spot determinations of plasma catecholamine levels, a weak correlation between these values and left ventricular measurements is not at all surprising. 2) Structural cardiac adaptation has been shown to be modified by the activity of the renin-angiotensin-aldosterone system, which is directly affected by sodium homeostasis. The fact that dietary salt loading suppresses the activity of the renin-angiotensin-aldosterone system seems at a first glance to be at variance with the present findings. However, this suppression is inadequate in nearly half of the population with essential hypertension. Inappropriately elevated angiotensin II levels could possibly account for the increase in left ventricular mass in this subpopulation. Such a view is supported by the findings of a preliminary study showing that angiotensin II was closely related to concentric left ventricular hypertrophy. The exact mechanisms by which angiotensin II influences myocardial growth remain unknown, although it is known to stimulate DNA, RNA, and protein synthesis in myocardial muscle cells. We have previously identified total blood volume as a determinant of left ventricular hypertrophy in a heterogeneous population of 171 patients. Sodium balance determines, at least to some extent, the intracellular and extracellular fluid volume state, and left ventricular dimensions have been shown to increase in healthy volunteers after 2 weeks on a high salt intake. Although the current study (in a smaller population) did not find any link between plasma or total blood volume and sodium excretion or left ventricular hypertrophy, it is conceivable that a high dietary salt intake accelerates myocardial hypertrophy by chronically expanding intravascular volume and thereby increasing preload to the left ventricle.

We conclude that among all examined clinical, hemodynamic and endocrine factors, dietary salt intake seems to be the strongest determinant for the degree of cardiac structural adaptation. The dietary sodium intake could influence cardiac adaptation by interacting with the renin-angiotensin-aldosterone system, with the sympathetic nervous system, or with fluid volume homeostasis. Whether dietary sodium restriction might prevent or at least mitigate the process of myocardial hypertrophy in essential hypertension remains unknown although preliminary results indicate that a strict sodium depletion could indeed reduce left ventricular mass in essential hypertension.

![Figure 2](image-url) Relation between sodium excretion and relative wall thickness.

![Figure 3](image-url) Relation between sodium excretion and left ventricular mass.
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