Participation of endogenous catecholamines in the regulation of left ventricular mass in progeny of hypertensive parents

BRUNO TRIMARCO, M.D., BRUNO RICCIARDELLI, M.D., NICOLA DE LUCA, M.D., ANTONIO DE SIMONE, M.D., ALBERTO CUOCOLO, M.D., MARIA D. GALVA, M.D., GIOVANNI B. PICOTTI, M.D., AND MARIO CONDORELLI, M.D.

ABSTRACT To investigate whether adrenergic activity is a determinant of left ventricular hypertrophy in human hypertension, in each of 10 normotensive subjects with two hypertensive parents we have examined the relationship between changes in echocardiographic parameters of left ventricular anatomy and those in circulating catecholamine levels induced by three, 3 week periods of different sodium and potassium intakes. A high sodium–normal potassium regimen induced a significant reduction in upright plasma norepinephrine (from 599 ± 89 to 379 ± 45 pg/ml, p < .01) and in posterior wall (PWT) and interventricular septal (IVST) thickness, as well as in the left ventricular mass index (LVMi). Changes in upright plasma norepinephrine concentrations correlated with those in IVST (r = .822, p < .01) and in LVMi (r = .833, p < .01). A low sodium–normal potassium diet resulted in increases in supine and upright plasma norepinephrine levels (from 356 ± 44 to 488 ± 89 pg/ml, p < .001; and from 565 ± 42 to 744 ± 33 pg/ml, p < .01) as well as increases in IVST and LVMi (from 97 ± 7 to 107 ± 7 mm², p < .001). The changes in norepinephrine levels in supine and upright subjects correlated with changes in IVST (r = .836, p < .01 and r = .796, p < .01) and in LVMi (r = .931, p < .001 and r = .947, p < .001). No significant change in plasma catecholamine concentrations or in PWT, IVST, or LVMi was detected after a low sodium–high potassium regimen. Blood pressure was essentially unchanged throughout the study. Furthermore, an ancillary study was performed in another nine normotensive subjects with hypertensive parents who underwent a reduction in dietary salt intake combined with therapy with the β-adrenoreceptor–blocking agent atenolol. In these patients the increase in supine and upright plasma norepinephrine concentrations were not accompanied by any increase in IVST, PWT, or LVMi. These findings indicate that in hypertensive progeny catecholamines play a role in the physiologic regulation of left ventricular mass.


ALTHOUGH recent evidence that the degree of hypertensive left ventricular hypertrophy is closely related to blood pressure1–6 seems to indicate that blood pressure levels are the main determinant of left ventricular mass (LVM), the possibility that other factors play a role in the control of LVM cannot be ruled out a priori. In spontaneously hypertensive rats, the participation of some humoral factors in the genesis of left ventricular hypertrophy has been supported by strong evidence.7–10 Regarding the sympathetic nervous system, a number of experimental studies indicate that catecholamines can induce cardiac hypertrophy.11,12 On the other hand, in human beings there is only indirect evidence to suggest that the sympathetic system may be involved in the control of LVM. Corea et al.13 reported that the increase in interventricular septal thickness (IVST) observed in borderline hypertensive subjects was not related to arterial pressure but rather to levels of plasma norepinephrine. More recently the same authors4 found that arterial pressure and plasma norepinephrine levels were both related to the degree of left ventricular hypertrophy in patients with stable arterial hypertension. Finally, we have previously reported that the changes in LVM observed in hypertensive patients during antihypertensive therapy with atenolol correlate with the changes in heart rate but not with those in arterial blood pressure.14
PATHOPHYSIOLOGY AND NATURAL HISTORY—HYPERTENSION

This study was aimed at investigating whether in human hypertension changes in sympathetic activity and thus in catecholamine release might induce changes in LVM. For this purpose, changes in dietary sodium intake were chosen as long-term influences on the sympathetic system to allow sufficient time for changes in LVM. Restriction of dietary sodium is known to increase plasma levels of norepinephrine, while there is a trend toward lower plasma norepinephrine after excessive sodium intake. Parallel changes in plasma epinephrine have also been reported.

In the present study, dietary sodium contents of 80 (low), 180 (normal), and 330 (high) meq/day were consumed.

Since in established hypertension, unlike in normotension, altered sodium intake is known to induce changes in blood pressure, to study the effects of changes in sympathetic activity on LVM without interference from pressure changes, we chose young normotensive subjects with first-degree relatives who had essential hypertension. There is a very high incidence of hypertension later in life in such individuals. Moreover, to exclude the possibility that changes in dietary sodium intake induce changes in LVM, if any, through mechanisms different from changes in sympathetic tone, we also attempted to reduce blood volume without increasing sympathetic tone by administering a low sodium—high potassium diet. Indeed, it has been shown that in the progeny of hypertensive patients a high potassium intake may prevent the increase in sympathetic activity induced by a low-sodium diet.

Subjects and methods

A group of 16 normotensive subjects, each with two parents with a history of essential hypertension and from 17 to 37 years old (mean age 27 ± 2 years) participated in the study. All subjects were fully informed about the procedure and the aim of the study, and written consent was obtained from each. None of the subjects had any abnormalities on admission screening that included physical examination, electrocardiography, M mode and two-dimensional echocardiography, chest x-ray and renography, hematologic profile, liver and renal function tests, tests for plasma aldosterone, plasma renin activity (supine and after 1 hr upright), and urinary vanillylmandelic acid and free catecholamine concentrations and a thyroid function test. Blood pressure was measured three times, at least a week apart, with the subjects in the supine position after 5 min of rest in a darkened room, with a mercury sphygmomanometer as recommended by the American Heart Association. Blood pressures of all subjects were in the normal range. None of them had taken any medication for at least a month preceding the study and none received medication during the period of the study.

In the month preceding the study, as well as during the study, each subject consumed a daily diet containing 80 meq sodium, 70 meq potassium, 65 g protein, 50 g fat, 270 g carbohydrate, and 100 mg phosphorus as meat, eggs, bread, vegetables, and fruit (this was the low-sodium regimen). Personal food preferences were allowed as much as possible. Furthermore, while on this diet, which was designed to minimize changes in body weight due to changes in food intake, all subjects were also given 100 meq/day of NaCl divided in two doses of 50 meq each wrapped in wafers. Water intake was allowed as desired. Twenty-four hour urine specimens were obtained on the last 3 days of this period to determine diuresis, natriuresis, and kaliuresis. Moreover, on the last day of this month, the subjects were asked to abstain from tobacco, coffee, tea, chocolate, strenuous physical activity, and sexual intercourse for at least 24 hr, as well as to fast and abstain from fluids for 12 hr. At 9 A.M. they were weighed after voiding and their blood pressures were measured both while they were supine and after they had been upright for 2 min. An indwelling cannula was then inserted into a vein of the antecubital fossa of the arm of each and a blood sample was taken after the subjects had been supine for at least 2 hr to determine levels of hematocrit, serum electrolytes, creatinine, plasma renin activity, aldosterone, epinephrine, and norepinephrine. Additional blood samples for determination of plasma catecholamine levels were also taken after subjects had been standing for 5 min. A further blood sample was taken after the subjects had been standing for 1 hr and plasma renin activity and aldosterone levels were determined. Finally, M mode and two-dimensional echocardiograms were obtained for the assessment of LVM. After these measurements, the subjects continued on the diet but with different supplements of NaCl and potassium as follows: (1) 330 meq/day NaCl and 70 meq/day potassium (diet plus 250 meq of crystalline sodium chloride), (2) 80 meq/day NaCl and 70 meq/day of potassium (diet with no salt supplementation) and (3) 80 meq/day of NaCl and 150 meq/day potassium (diet plus 80 meq/day potassium). Each of the three regimens was followed for 3 weeks.

At the end of each period, all the measurements were repeated as previously described. The subjects were then given the standard diet supplemented with 100 meq of NaCl until the echocardiographic LVM returned to the basal level (about 3 weeks). A new set of measurements was then obtained and a different sodium regimen was instituted for 3 weeks. The order in which the diets were administered to each subject was according to a computer-based randomization scheme. The supplementation to the diet in period 1 was accomplished by adding five doses of 50 meq crystalline NaCl wrapped up by wafers and in period 3, 10 slow-release tablets of KCl containing 8 meq of potassium each, divided into five doses, were given.

To further investigate the relationship between catecholamines and LVM, we performed an ancillary study in 10 normotensive subjects (five men and five women), who with two parents with a history of essential hypertension, who were from 15 to 33 years old (mean 24 ± 3 years). They were asked to follow the same guidelines pertaining to diet, personal habits, and drug intake as those in the other group. The subjects were initially studied under control conditions. The same procedures were followed as in the previous study, both on the test day and on the days before the testing procedure. The daily supplement of 100 meq sodium chloride was then withdrawn and the subjects received 80 meq/day NaCl and 70 meq/day of potassium over 3 weeks. During this period they were also given the β-adrenoreceptor blocker atenolol (100 mg orally once a day). At the end of the 3 weeks the subjects were studied again.

Finally, the reproducibility of echocardiographic measurements was tested in a parallel series of 10 normal subjects studied three times with the same ultrasonic technique under the same conditions; an interval of 3 weeks was allowed between the first and second study and 2 months elapsed between the second and third study. Under these circumstances, the coefficient of variation for LVM was 4.1%.

Analyses. Blood pressure was measured by a standard sphyg-
momanometer. Urinary and serum electrolytes were measured with a flame photometer. Creatinine was measured by an automated technique. Epinephrine and norepinephrine were measured simultaneously in 50 μl of plasma by a sensitive and specific radioenzymatic technique, as previously described. Plasma renin activity was measured by the method of Menard and Catt (sensitivity 5 ± 0.4 pg/tube angiotensin I; i.e., PRA = 0.06 ng/ml/hour) and plasma aldosterone concentration by the method of McKenzie and Clements (sensitivity 6 ± 1 pg/ml). M mode echocardiography was performed with standard techniques previously reported from this laboratory and images were obtained under sector-scanning monitoring to detect the occurrence of any change in left ventricular shape and to avoid angulation of the ultrasonic beam. Echocardiographic tracings were coded and read blind and in random order by two expert observers blinded to the protocol. End-diastolic measurements of IVST, left ventricular internal dimension (LVID), and posterior wall thickness (PWT) were made according to the Penn convention protocol to measure LVM. This was calculated by the simple and anatomically validated formula LVM = 1.04 ((IVST + LVID + PWT)³ - LVID³) - 13.6. To minimize the impact of variation in body size on LVM, it was corrected for body surface area. End-diastolic and end-systolic measurements were also made according to the recommendations of the American Society of Echocardiography.

Changes in plasma volume were estimated from the changes in peripheral microhematocrits with the formula: P = 100/(100 - Ht) 100 (Ht - H1/H2), in which P is the percent change in plasma volume and H1 and H2 are the initial and the final packed cell volumes.

**Statistical analysis.** The Student t test was used to compare pre- and postdiet values of the different parameters. The strength of the association between the changes in various parameters and those in LVM index (LVMi) and IVST was assessed by the product moment correlation coefficient and its test of significance. Differences between the values for each parameter in the same subject under different circumstances were assessed by Student’s t test for paired data.

**TABLE 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase 1 Before</th>
<th>Phase 1 After</th>
<th>Phase 2 Before</th>
<th>Phase 2 After</th>
<th>Phase 3 Before</th>
<th>Phase 3 After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume</td>
<td>13.8 ± 6.7</td>
<td>-9.8 ± 4.6</td>
<td>1344 ± 187</td>
<td>-10.2 ± 5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuresis (ml)</td>
<td>1372 ± 168</td>
<td>1661 ± 204</td>
<td>1344 ± 187</td>
<td>1673 ± 251</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>70.7 ± 2.8</td>
<td>71.4 ± 2.9</td>
<td>70.6 ± 1</td>
<td>69.8 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Na⁺ (meq/l)</td>
<td>144 ± 2</td>
<td>147 ± 1</td>
<td>145 ± 2</td>
<td>148 ± 2</td>
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<td></td>
</tr>
<tr>
<td>Serum K⁺ (meq/l)</td>
<td>4.2 ± 0.1</td>
<td>4.4 ± 0.2</td>
<td>4.4 ± 0.1</td>
<td>4.7 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Na⁺ (meq/24 hr)</td>
<td>129 ± 6</td>
<td>305 ± 9b</td>
<td>131 ± 6</td>
<td>69 ± 5b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary K⁺ (meq/24 hr)</td>
<td>61 ± 6</td>
<td>68 ± 3</td>
<td>64 ± 4</td>
<td>126 ± 11b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA supine (ng/ml/hr)</td>
<td>0.96 ± 0.1</td>
<td>0.47 ± 0.1b</td>
<td>1.2 ± 0.1</td>
<td>1.5 ± 0.1b</td>
<td></td>
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<tr>
<td>PRA upright (ng/ml/hr)</td>
<td>1.6 ± 0.1c</td>
<td>0.77 ± 0.1b</td>
<td>2.0 ± 0.1c</td>
<td>2.2 ± 0.1c</td>
<td></td>
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<tr>
<td>Aldosterone supine (pg/ml)</td>
<td>217 ± 31</td>
<td>145 ± 24b</td>
<td>166 ± 16</td>
<td>211 ± 29a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone upright (pg/ml)</td>
<td>314 ± 34c</td>
<td>209 ± 33b</td>
<td>270 ± 17c</td>
<td>331 ± 19bc</td>
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<td></td>
</tr>
</tbody>
</table>

Means ± SE for 10 subjects.

*Ap < .05 and p < .01, respectively, for values obtained before vs after each diet.

*Cp < .05 for supine vs upright values.

**Results**

Six subjects were excluded from the study: two did not complete the protocol and in four urinary sodium and/or potassium excretion did not match the calculated intake. The data for the remaining 10 subjects are listed in tables 1 to 3. There were no differences in the basal values of the various parameters at any time in the study. The accuracy of the echocardiographic measurements was indicated by the observation that blind readings by two independent trained observers varied by 1 mm or less and also by comparing LVM at end-diastole and at end-systole in each echocardiographic tracing; the correlation coefficient varied between .9 and .98. No change in left ventricular shape was detected by two-dimensional echocardiography throughout the study.

**Phase 1 (high sodium/normal potassium intake).** During this phase serum sodium and potassium levels remained unchanged, while there were significant increases in urinary sodium output, body weight, and plasma volume (table 1). There was no change in systolic or diastolic blood pressure (table 2). Upright heart rate fell significantly (table 2): the response to standing was reduced from +12 ± 2 to +7 ± 2 beats/min (p < .001). Furthermore, there were significant decreases in both supine and upright plasma renin activity and plasma aldosterone concentrations (table 1). Upright plasma epinephrine and norepinephrine concentrations were also significantly reduced (table 3). LVMi decreased from 98 ± 6 to 88 ± 6 g/m² (p <
TABLE 2
Supine and upright systolic and diastolic blood pressures (BPs) and heart rates, IVST and PWT, LVID and LVMi before and after three different sodium and potassium diets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP supine (mm Hg)</td>
<td>1</td>
<td>128±4</td>
<td>122±3</td>
<td>128±2</td>
<td>121±6</td>
<td>123±5</td>
<td>118±6</td>
</tr>
<tr>
<td>Systolic BP upright (mm Hg)</td>
<td>2</td>
<td>133±4</td>
<td>126±3</td>
<td>127±3</td>
<td>125±5</td>
<td>126±5</td>
<td>121±6</td>
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<tr>
<td>Diastolic BP supine (mm Hg)</td>
<td></td>
<td>79±1</td>
<td>81±2</td>
<td>80±1</td>
<td>78±2</td>
<td>80±2</td>
<td>75±3</td>
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<td>Diastolic BP upright (mm Hg)</td>
<td>3</td>
<td>87±2</td>
<td>88±2</td>
<td>88±2</td>
<td>86±3</td>
<td>85±4</td>
<td>81±4</td>
</tr>
<tr>
<td>Heart rate supine (bpm)</td>
<td>1</td>
<td>67±3</td>
<td>63±3</td>
<td>67±2</td>
<td>74±3A</td>
<td>66±4</td>
<td>68±4</td>
</tr>
<tr>
<td>Heart rate upright (bpm)</td>
<td>2</td>
<td>79±4C</td>
<td>70±3B</td>
<td>76±3C</td>
<td>85±4</td>
<td>78±5C</td>
<td>81±3E</td>
</tr>
<tr>
<td>IVST (cm)</td>
<td></td>
<td>0.81±0.03</td>
<td>0.75±0.03A</td>
<td>0.803±0.03</td>
<td>0.844±0.03A</td>
<td>0.813±0.03</td>
<td>0.795±0.02</td>
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<tr>
<td>PWT (cm)</td>
<td></td>
<td>0.79±0.03</td>
<td>0.73±0.03B</td>
<td>0.822±0.04</td>
<td>0.833±0.04</td>
<td>0.791±0.03</td>
<td>0.807±0.03</td>
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<tr>
<td>LVID (cm)</td>
<td></td>
<td>5.19±0.14</td>
<td>5.14±0.15</td>
<td>5.0±0.14</td>
<td>5.0±0.10</td>
<td>5.11±0.13</td>
<td>4.98±0.11</td>
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<tr>
<td>LVMi (g/m²)</td>
<td></td>
<td>98±6</td>
<td>88±6B</td>
<td>97±7</td>
<td>107±7B</td>
<td>97±6</td>
<td>94±6</td>
</tr>
</tbody>
</table>

Means ± SE for 10 subjects.  
A,Bp < .05 and p < .01, respectively, for values obtained before vs after each diet.  
Cp < .05 for supine vs upright values.

.01), IVST fell from 0.81 ± 0.03 to 0.75 ± 0.03 cm (p < .05), and PWT decreased from 0.79 ± 0.03 to 0.73 ± 0.03 cm (p < .01), while LVID remained unchanged (table 2). The changes in LVMi and IVST were significantly correlated with those in upright plasma norepinephrine concentration (figure 1).

Phase 2 (low sodium/normal potassium intake). In this phase also serum sodium and potassium levels remained unchanged, but we observed falls in sodium output, body weight, and plasma volume (table 1). No significant changes in systolic and diastolic blood pressures were seen, while heart rate increased in these subjects in both the supine and upright positions (table 2). Plasma renin activity and aldosterone concentrations and plasma norepinephrine increased significantly in both the supine and upright positions (tables 2 and 3). There were no significant changes in epinephrine plasma levels (table 3). In this phase there were significant increases in IVST (from 0.8 ± 0.03 to 0.84 ± 0.03 cm, p < .05) and LVMi (from 97 ± 7 to 107 ± 7 g/m², p < .001), but not in LVID (table 2). These changes correlated with the changes in plasma norepinephrine levels in subjects in both the upright and supine positions (figures 2 and 3).

TABLE 3
Supine and upright plasma epinephrine and norepinephrine levels before and after the three different sodium and potassium diets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine supine</td>
<td>1</td>
<td>31±4</td>
<td>29±5</td>
<td>26±5</td>
<td>30±6</td>
<td>27±6</td>
<td>20±3</td>
</tr>
<tr>
<td>Epinephrine upright</td>
<td>2</td>
<td>34±3</td>
<td>20±5B</td>
<td>35±6</td>
<td>35±8</td>
<td>35±6</td>
<td>37±12</td>
</tr>
<tr>
<td>Norepinephrine supine</td>
<td>3</td>
<td>306±45</td>
<td>272±38</td>
<td>356±44</td>
<td>488±49B</td>
<td>298±49</td>
<td>226±20</td>
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<tr>
<td>Norepinephrine upright</td>
<td></td>
<td>599±89D</td>
<td>379±45R,C</td>
<td>565±42D</td>
<td>744±33R,C</td>
<td>581±113C</td>
<td>571±56D</td>
</tr>
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</table>

Means ± SE for 10 subjects.  
A,Bp < .05 and p < .01, respectively, for values obtained before vs after each diet.  
C,Dp < .05 and p < .01, respectively, for supine vs upright values.
Phase 3 (low sodium/high potassium intake). In this period we found a significant increase in serum potassium and in kaliuresis, a decrease in natriuresis, body weight, and plasma volume, and no change in serum sodium concentration (table 1). In this case the reduction in plasma volume was not accompanied by any significant increase in heart rate (table 2). Systolic and diastolic blood pressure remained unmodified, while plasma renin activity and plasma aldosterone concentration rose significantly (table 1). In this period we saw no significant change in plasma catecholamine levels (table 3) or in the echocardiographic parameters of left ventricular anatomy (table 2).

Study with atenolol. One subject was excluded from this study because his sodium excretion did not match the calculated intake. The data for the remaining nine subjects are listed in table 4. Under control conditions, no significant differences were detectable for any of the considered parameters between the subjects enrolled in this study and those participating in the study previously described. In the atenolol study, the effects of low sodium intake on blood pressure, sodium and
potassium output, body weight, and plasma volume (−13.3 ± 4%, p < .01) were similar to those observed in phase 2 of the previous study (table 4). As expected, the changes in plasma renin activity and aldosterone concentrations induced by low sodium intake in subjects in both the supine and upright positions (data not shown), as well as the heart rate response to standing (table 4), were markedly blunted by atenolol. On the other hand, the pharmacologic blockade of β-

**TABLE 4**

**Effects of low sodium-normal potassium diet and atenolol (100 mg orally once a day) on physical, humoral, and echocardiographic parameters**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
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<tr>
<td>Body weight (kg)</td>
<td>69 ± 3</td>
<td>68 ± 3 a</td>
</tr>
<tr>
<td>Urinary Na+ (meq/24 hr)</td>
<td>131 ± 3.3</td>
<td>61 ± 2.6 b</td>
</tr>
<tr>
<td>Urinary K+ (meq/24 hr)</td>
<td>69 ± 4.5</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>MAP supine (mm Hg)</td>
<td>98 ± 3</td>
<td>97 ± 2</td>
</tr>
<tr>
<td>MAP upright (mm Hg)</td>
<td>103.6 ± 2.2</td>
<td>101.1 ± 2.1</td>
</tr>
<tr>
<td>Heart rate supine (bpm)</td>
<td>65 ± 6</td>
<td>57 ± 5 b</td>
</tr>
<tr>
<td>Heart rate upright (bpm)</td>
<td>82.4 ± 8.2 b</td>
<td>66.6 ± 7.8 b,c</td>
</tr>
<tr>
<td>Norepinephrine supine (pg/ml)</td>
<td>257 ± 36</td>
<td>356 ± 38 a</td>
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<tr>
<td>Norepinephrine upright (pg/ml)</td>
<td>395 ± 47 c</td>
<td>587 ± 35 b,d</td>
</tr>
<tr>
<td>IVST (cm)</td>
<td>0.83 ± 0.03</td>
<td>0.83 ± 0.05</td>
</tr>
<tr>
<td>PWT (cm)</td>
<td>0.87 ± 0.04</td>
<td>0.86 ± 0.04</td>
</tr>
<tr>
<td>LVID (cm)</td>
<td>5.22 ± 0.21</td>
<td>5.13 ± 0.21</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>102 ± 8.3</td>
<td>99 ± 9</td>
</tr>
</tbody>
</table>

Mean ± SE for nine subjects.

MAP = mean arterial pressure.

a,b p < .05 and p < .01, respectively, for values obtained before vs after each diet.

Discussion

Recent reports from several groups have shown that increased blood pressure is probably the main determinant of hypertension-induced left ventricular hypertrophy. Therefore, when testing the possibility that other factors are involved in the control of LVM in human hypertension, it is necessary to keep arterial blood pressure constant when the variable being investigated changes. In this study, lasting changes in sympathetic activity without any blood pressure change were obtained by exposing normotensive offspring of hypertensive parents to different sodium intakes. Pressure changes would be anticipated if patients with established hypertension were exposed to analogous situations. It should be noted that in animal experiments LVM has been shown to be greater in spontaneously hypertensive rats than in normotensive rats in which renal hypertension was produced by unilateral arterial obstruction when they were exposed to the same pressure load. Although a similar finding has not been reported for humans, studies in normotensive subjects may not be suitable for investigating the mechanisms.
controlling LVM in hypertensive patients. However, it has been demonstrated\(^1\) that the incidence of hypertension in offspring is 46% when both parents are hypertensive, 28% if one parent is hypertensive, and only 3% if neither parent is hypertensive. Therefore, normotensive subjects with two hypertensive parents, a population with a very high incidence of hypertension, offer the best opportunity for studying essential hypertension at its inception.

In our subjects, changes in dietary sodium intake did not induce any significant change in blood pressure, but did modify LVM.

Low sodium intake induced a 10% increase in LVM and high sodium intake was accompanied by a decrease in LVM of a similar magnitude. Both of these changes were reversed when sodium intake was returned to normal. In particular, the changes in LVM seem to be exclusively due to changes in left ventricular wall thickness since LVID remained unchanged throughout the study.

The first question raised by these results is the reliability of echocardiographic LVM measurement. It has been reported that echocardiography can repeatedly\(^2\) and accurately\(^3\) quantify the thickness of ventricular walls as well as the LVM. However, echocardiographic calculation of LVM requires many assumptions, the least well proved of which is that the longitudinal axis of the left ventricle is always twice as much as the anteroposterior or transverse diameter, which may not apply in hearts affected with a configuration-altering disease.\(^4\) However, the present study includes relatively young patients with no history, symptoms, or signs of myocardial damage and who, therefore, can be assumed to have symptomically contracting ventricles. Furthermore, in this study, changes in wall thickness and LVM were in the same direction, suggesting that the changes in LVM reflected changes in wall thickness more than changes in left ventricular volume.

The second consideration with regard to our results is that the magnitude of the changes in LVM, in both directions, were about 10% of the basal values. These are smaller than those obtained with antihypertensive therapy in patients with established hypertension.\(^5\) However, this discrepancy is not surprising since the follow-up periods in those studies were longer than ours. Furthermore, hypertensive individuals have greater LVM than our subjects, who were still normotensive, and it has been demonstrated\(^6\) that there is a significant correlation between the initial LVM and the magnitude of the change in this parameter induced by therapy.

In agreement with previous reports,\(^7\) low sodium intake was accompanied by an increase in plasma renin activity and plasma aldosterone and catecholamine concentrations, while opposite changes were observed during high sodium intake. Only the changes in plasma norepinephrine were found to be correlated with the changes in left ventricular anatomy, suggesting that the sympathetic system may play a role in the control of LVM in hypertensive patients. In fact, plasma norepinephrine concentration has been demonstrated to reflect the averaged contribution from the various vascular beds and, therefore, to be an index of overall sympathetic nervous activity.\(^8\) The observation that the changes in plasma norepinephrine are accompanied by concomitant changes in heart rate documents the importance of catecholamine measurement as an index of the cardioadrenergic drive.

It should be noted that the correlation between changes in plasma norepinephrine and LVM does not allow us to rule out a direct effect of sodium per se on LVM.

The observation that a high potassium intake abolishes the increase in sympathetic tone induced by a low-sodium diet is in agreement with the findings of Parfrey et al.\(^9\) in young subjects with a familial predisposition to hypertension. The mechanisms that underly this phenomenon are still unclear: both a genetically determined and specific effect of potassium on sympathetic activity\(^10\) and an effect of external potassium concentration on the Na\(^+\)-K\(^+\) pump\(^11\) have been postulated. However it works, the observation that sodium restriction is unable to induce any change in LVM when the increase in sympathetic tone is prevented seems to corroborate the hypothesis that there is a cause-effect relationship between the changes in sympathetic nervous activity, as reflected by plasma norepinephrine concentration, and those in LVM induced by low sodium intake. The results obtained by administration of atenolol lend further support to this hypothesis. In fact, we were able to prevent the increase in left ventricular wall thickness and, consequently, in LVM induced by a reduction in dietary sodium intake by protecting the heart from the effects of an increased adrenergic drive. Although it has been previously reported that norepinephrine administered to dogs\(^12\) and rats\(^13\) in subhypertensive doses evokes myocardial hypertrophy, this study presents the first data showing that changes in norepinephrine levels within the physiologic range are related to changes in LVM in normotensive subjects who are first-degree relatives of patients with essential hypertension without changes in blood pressure. The present study does not, however,
elucidate the precise role of the adrenergic influence of LVM. The observation that changes in sympathetic activity are always accompanied by concomitant changes in heart rate suggests that hemodynamic factors mediate the observed changes in LVM, as has been found in young spontaneously hypertensive rats and in early phases of human hypertension. However, changes in systemic hemodynamics might not be the only way whereby catecholamines are related to changes in ventricular weight, since catecholamines have been shown to facilitate the incorporation of amino acids into myocardial and vascular proteins.

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