Left Ventricular Mass Reduction During Salt Depletion in Arterial Hypertension

L. ALDO FERRARA, GIOVANNI DE SIMONE, FABRIZIO PASANISI, MARCELLO MANCINI, AND MARIO MANCINI

SUMMARY Long-term therapy with antihypertensive agents that reduce sympathetic nervous system activity has been demonstrated by echocardiographic measurements to reverse left ventricular hypertrophy. This investigation evaluated the effects of salt depletion obtained by both chlorthalidone (25 mg/day) and severe restriction of salt intake (about 1016 mg Na\(^+\)/day) on left ventricular mass (LVM) in as short a time as 12 weeks. Before the study, the patients had been off medication and on a balanced diet without salt restriction for at least 2 weeks; they were then randomly allocated to either the diuretic or low-salt regimen for 6 weeks and finally to alternative treatment according to a crossover model. Blood pressure, body weight, myocardial mass, and noninvasive measurements of left ventricular function (LVF) were determined at baseline and at the end of both periods of treatment. Results were evaluated by two-way analysis of variance in randomized blocks. Systolic and diastolic blood pressure and LVM were significantly and similarly reduced by diuretic therapy or salt restriction. A significant correlation was demonstrated between noninvasive measurements of LVM, expressed as cross-sectional area, and systolic blood pressure. No impairment of LVF could be detected over the treatment period. (Hypertension 6: 755-759, 1984)

KEY WORDS • left ventricular hypertrophy • diuretic therapy • severe salt intake restriction

LEFT ventricular hypertrophy (LVH) is a frequent complication of arterial hypertension. The effects of antihypertensive treatment on left ventricular mass (LVM) have long been studied by electrocardiogram (ECG) and x-ray. These measurements, however, are poorly correlated with angiographically or anatomically determined LVM. Only echocardiography has provided noninvasive, quantitative, reproducible measurements of LVM that are well correlated with invasive assessments. Data on reversal of LVH during long-term antihypertensive therapy are now available mainly after treatment with agents, like methyldopa, which reduce sympathetic nervous system activity. On the other hand, no effect on LVH has been demonstrated with vasodilators, like hydralazine, which enhance reflex sympathetic outflow.

The aim of this study was to evaluate the effect of short-term (12-week) salt depletion on blood pressure (BP) and LVM in hypertensive patients and to compare the effects of chlorthalidone therapy with those of severe restriction of salt intake.

Patients and Methods

Patients

Ten men seen in our outpatient clinic for inadequately controlled primary hypertension comprised the study group. Criteria for inclusion were: 1) arterial hypertension of mild to moderate degree, with a diastolic blood pressure (DBP) between 94 and 114 mm Hg on two or more separate examinations; 2) absence of signs of target organ damage; 3) absence of heart failure or other cardiac disease other than arterial hypertension; 4) absence of nonuniform septal thickness assessed by prestudy B-mode echocardiography; and 5) age range between 25 and 50 years.

Methods

Patients with other chronic diseases were excluded from the study. The protocol was fully explained to all the participants, and their informed consent was obtained. An isocaloric well-balanced diet (2000 Kcal/day) without any salt restriction was prescribed for a period of 2 weeks. Antihypertensive or other medications that could interfere with BP regulation were discontinued. Clinical examination was then repeated at the end of the run-in period, and the following measurements were made.

Left Ventricular Cross-Sectional Area and Mass

Left ventricular (LV) cross-sectional area (CSA) and echocardiographic LVM (LVM\(_E\)) was measured by standard M-mode echocardiography (ME) accord-
ing to Devereux and Reichel. The LV dimensions were measured at the level of the chordae tendineae of the mitral valve. Interventricular septal thickness (ST), posterior wall thickness (PWT), and end-diastolic diameter (EDD) were determined by using the Penn convention to calculate LVM, and by using standard convention to calculate CSA. Cross-sectional area was calculated as the area within a hypothetical circle with a diameter equal to the sum of EDD plus ST plus PWT and subtracting the area of a circle with a diameter equal to EDD alone. This index has been shown to correlate highly with LVM and to accurately reflect changes in the myocardial mass. The echocardiograms were obtained with a manual scan echocardiograph (Sonia, CGR, France) with a 2.25 mHz transducer. The images have been printed both on Polaroid film and on Ilford x-ray film (CIBA, England). Echocardiograms were numerically coded and independently read in a random sequence by two experienced observers. Only when LV dimension could have been determined with reasonable certainty and both ST and PWT could have been well demonstrated was ME considered suitable for the study. The measurements of each observer were the mean of two different complex readings. For each echocardiogram, technical error between the two readers’ measurements was calculated by the formula: 

\[
\text{error} = \frac{1}{2N} \sum_{i=1}^{N} \left| d_i \right|
\]

where \(d_i\) is the difference between a split pair and \(N\) is the number of pairs. The results are expressed as absolute value (error) and as percentage of the sample mean (percentage error).

### Abbreviations

- **BP**: blood pressure
- **CSA**: cross-sectional area
- **DBP**: diastolic blood pressure
- **ECG**: electrocardiogram
- **EDD**: end-diastolic diameter
- **EDV**: end-diastolic volume
- **EF**: ejection fraction
- **ESD**: end-systolic diameter
- **ESV**: end-systolic volume
- **ET**: ejection time
- **HR**: heart rate
- **LV**: left ventricular
- **LVF**: left ventricular function
- **LVH**: left ventricular hypertrophy
- **LVM**: left ventricular mass
- **LVMₑ**: echocardiographic left ventricular mass
- **MAP**: mean arterial blood pressure
- **ME**: M-mode echocardiography
- **PEP**: preinjection period
- **PWT**: posterior wall thickness
- **STI**: systolic time interval
- **SWI**: stroke work index
- **Vcf**: velocity of circumferential fiber shortening

### Left Ventricular Function

Left ventricular function was evaluated by noninvasive procedures that included measurement of LV ejection fraction (EF), which is the ratio of calculated LV stroke volume to end-diastolic volume (EDV) \(\times 100\), where volume was calculated by the formula: 

\[
V = \frac{7 \times \text{DV}^2.4 + D}{\text{EDD} \times \text{EDD}}
\]

in which D is the LV diameter. The mean rate of circumferential fiber shortening (Vcf) was calculated as: 

\[
\text{Vcf} = \frac{\text{EDD} - \text{ESD}}{\text{EDD}} \times \text{EDD} \times \text{EDD}
\]

Linear regression analysis was performed where indicated. The systolic time interval (STI) was calculated as the Weissler index (preinjection time [PEP] to LVET ratio) by a simultaneous phonocardiogram, electrocardiogram, and external-carotid-pulse tracing at a paper speed of 100 mm/sec.

### Cardiac Function

Cardiac work was expressed as stroke work index (SWI) by the formula: 

\[
\text{SWI} = \text{stroke index (SI)} \times \text{mean arterial pressure (MAP)} \times 0.0136.
\]

### Protocol

The patients were randomly allocated either to thiazide therapy (chlorthalidone 25 mg/day) or to normocaloric diet with severe salt restriction (about 1016 mg Na+/day) for a period of 6 weeks. The compliance to low salt diet has been evaluated measuring 24-hour urinary sodium excretion at baseline and after 3 and 6 weeks of diet. This period was followed by a second 6-week period of therapy during which the patients changed treatment in a cross-over model. The measurements performed at baseline were repeated at the end of each treatment.

### Statistical Analysis

Data are expressed as mean values \(\pm\) standard deviation (SD). Statistical significance was determined by using randomized blocks and two-way analysis of variance with Tukey’s multiple comparisons. Linear regression analysis was performed where indicated.

### Results

The mean age of patients was 39.7 \(\pm\) 6.7 years. Compliance with salt restriction was evaluated by 24-hr urinary sodium excretion, which decreased from 104.6 \(\pm\) 16.2 mEq/24 hr at baseline to 41.3 \(\pm\) 9.4 mEq/24 hr at the 3rd week, and to 29.7 \(\pm\) 4.7 mEq/24 hr at the 6th week of low salt intake.

The SBP and DBP were significantly reduced at the end of therapy; SBP was also reduced at the end of the first phase in both treatments. Body weight decreased slightly but not significantly over the 12 weeks of controlled therapy. No difference between groups in these parameters could be detected by statistical analysis (Table I).

Echocardiographic measurements of LVM showed a marked, significant reduction in CSA and LVMₑ, clearly detectable after the first 6 weeks of treatment and still observed to the same degree during the second period of both treatments. A very close relationship between the two noninvasive determinations of LVM (\(r = 0.957\)) was detected by linear regression analysis.
TABLE I. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and Body Weight (BW) at Baseline and at the End of Each Phase of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 weeks</th>
<th>12 weeks</th>
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<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>163.0±8.6</td>
<td>149.4±11.7*</td>
<td>143.0±8.8t</td>
</tr>
<tr>
<td>Diuretic</td>
<td>158.0±8.1</td>
<td>143.0±7.9t</td>
<td>137.4±8.1t</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>109.0±8.5</td>
<td>99.6±12.0</td>
<td>95.8±11.2*</td>
</tr>
<tr>
<td>Diuretic</td>
<td>104.2±5.5</td>
<td>95.2±7.0</td>
<td>90.0±5.4*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>74.4±7.9</td>
<td>75.6±9.2</td>
<td>74.0±12.4</td>
</tr>
<tr>
<td>Diuretic</td>
<td>72.0±8.5</td>
<td>73.2±9.7</td>
<td>71.6±9.5</td>
</tr>
<tr>
<td>BW (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>79.6±7.2</td>
<td>76.7±9.0</td>
<td>74.9±8.1</td>
</tr>
<tr>
<td>Diuretic</td>
<td>75.4±6.2</td>
<td>73.9±4.6</td>
<td>73.6±4.7</td>
</tr>
</tbody>
</table>

Salt-restricted refers to the group that started the first 6 weeks with salt restriction, and Diuretic refers to the group that started with diuretics.

*p < 0.05; significant results, treatment vs baseline

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>24.4±1.9</td>
<td>20.3±1.4*</td>
<td>19.2±1.9*</td>
</tr>
<tr>
<td>Diuretic</td>
<td>23.4±4.8</td>
<td>19.7±3.3*</td>
<td>19.3±2.5*</td>
</tr>
<tr>
<td>LVM (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>235.5±40</td>
<td>178.4±30*</td>
<td>167.3±34*</td>
</tr>
<tr>
<td>Diuretic</td>
<td>223.3±71</td>
<td>177.3±42*</td>
<td>166.6±37*</td>
</tr>
<tr>
<td>PWT + ST (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>2.60±0.2</td>
<td>2.30±0.1*</td>
<td>2.21±0.1*</td>
</tr>
<tr>
<td>Diuretic</td>
<td>2.49±0.4</td>
<td>2.24±0.03</td>
<td>2.20±0.2*</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>2.9±0.6</td>
<td>2.7±0.4</td>
<td>2.7±0.4</td>
</tr>
<tr>
<td>Diuretic</td>
<td>3.1±0.4</td>
<td>2.9±0.3</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>4.7±0.6</td>
<td>4.4±0.5</td>
<td>4.4±0.5</td>
</tr>
<tr>
<td>Diuretic</td>
<td>4.7±0.4</td>
<td>4.5±0.2</td>
<td>4.4±0.2</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>38.5±14.6</td>
<td>33.7±8.6</td>
<td>342±9.5</td>
</tr>
<tr>
<td>Diuretic</td>
<td>37.1±20.3</td>
<td>29.9±11.3</td>
<td>29.3±11.8</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt restricted</td>
<td>105.0±33.7</td>
<td>93.2±28.8</td>
<td>91.4±27.1</td>
</tr>
<tr>
<td>Diuretic</td>
<td>105.2±20.3</td>
<td>96.2±12.4</td>
<td>94.8±12.5</td>
</tr>
</tbody>
</table>

*p < 0.05; significant results, treatment vs baseline.

Changes in LVM, expressed as CSA, in each patient during treatment are shown in Figure 1. Moreover, other indexes of LVM (PWT and ST) were reduced by both antihypertensive therapies (Figure 2).

Mean values in the two subgroups of CSA, LVM, PWT + ST, ESD, EDD, EDV, and end systolic volume (ESV) are shown in Table 2.
Indexes of cardiac function including EF, Vcf, and PEP-to-LVET ratio were unchanged by treatments. Stroke work was slightly decreased by both treatments (Table 3).

Linear regression analysis showed a significant correlation of CSA with both systolic (r = 0.406; p < 0.05) and MAP (r = 0.334; p < 0.05), but failed to demonstrate a correlation between DBP and CSA (r = 0.297). Finally, a highly significant correlation was demonstrated between baseline CSA and its reduction at the end of the treatment, expressed as percentage of the baseline value (Figure 3).

Technical error determined for CSA (to evaluate reproducibility of echocardiography measurements) was 0.44 as an absolute value (2.4% when expressed as a percentage of the sample mean).

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Work Index (SWI) (g/m²/beat)</td>
<td>Salt restricted</td>
<td>65 ± 16.8</td>
<td>55.8 ± 12.8</td>
</tr>
<tr>
<td></td>
<td>Diuretic</td>
<td>65.6 ± 19.9</td>
<td>58.6 ± 7.2</td>
</tr>
<tr>
<td>Ejection Fraction (EF)(%)</td>
<td>Salt restricted</td>
<td>65.9 ± 12.6</td>
<td>68.8 ± 5.9</td>
</tr>
<tr>
<td></td>
<td>Diuretic</td>
<td>63.4 ± 8.4</td>
<td>65.2 ± 5.5</td>
</tr>
<tr>
<td>Mean Velocity of Circumferential Fiber Shortening (Vcf) (circ-sec)</td>
<td>Salt restricted</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Diuretic</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>Salt restricted</td>
<td>0.31 ± 0.03</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>Diuretic</td>
<td>0.31 ± 0.04</td>
<td>0.31 ± 0.05</td>
</tr>
</tbody>
</table>

### References

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**FIGURE 3. Correlation between left ventricular cross-sectional area at baseline and the percentage of its decrease at the end of treatment.**
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