Time course of regression of left ventricular hypertrophy in hypertensive patients treated with atenolol

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ABSTRACT Regression of left ventricular hypertrophy occurs with a number of antihypertensive drugs, but the time course of this regression has not been defined clearly. We obtained echocardiograms at baseline and serially (on seven occasions) during a 1 year treatment period with the ß-adrenergic receptor inhibitor atenolol in 12 patients with previously untreated essential hypertension. To ensure control of blood pressure in all patients throughout the study, it was necessary to add a thiazide diuretic to the therapy of five patients. Baseline blood pressure was 155/100 mm Hg and fell to 136/84 mm Hg; there was a 20% reduction in heart rate. Posterior and septal wall thicknesses were reduced from 1.16 ± 0.03 to 1.06 ± 0.02 cm (p < .05) and from 1.28 ± 0.07 to 1.18 ± 0.06 cm (p < .05), respectively; this reduction became significant initially at 4 weeks. Left ventricular mass decreased from 144 ± 9 to 127 ± 7 g/m² (p < .05) and this fall first became statistically significant at 6 months. Significant reduction in electrocardiographic voltages was also seen at 6 months. Therefore, regression of left ventricular hypertrophy with atenolol-induced blood pressure control occurred as early as 4 weeks after starting therapy and was maintained thereafter without apparent compromise of left ventricular systolic function.


A CONSIDERABLE AMOUNT of evidence has accumulated over the past 10 years with regard to regression of left ventricular hypertrophy (LVH) or mass in both experimental forms of hypertension and in patients with essential hypertension. Of particular interest is the fact that antihypertensive drugs are by no means uniform in their ability to diminish left ventricular mass and wall thickness. With some agents it is possible to achieve this with doses that do not reduce blood pressure, whereas others lower pressure effectively and yet do not cause a decrease in left ventricular mass. Despite the extensive literature, very little is known about the time course of this regression. Therefore, this study was designed to determine the time course of regression by the use of serial electrocardiography and echocardiography in a group of patients with essential hypertension, and also to establish whether this regression could be maintained with long-term control of blood pressure.

Methods

Patients. Fifteen patients (six white men, five black men, and four black women) with established hypertension are the subjects of this report. Three of these patients failed to complete the study; therefore, this analysis is confined to the remaining 12. Their mean age was 44 years (range 28 to 54). All had either never received antihypertensive therapy or had received only a thiazide diuretic that was discontinued before the study began. Patients who had received any other antihypertensive agent known to cause regression of hypertrophy were excluded from this study. No patient had ever been in cardiac failure. Six patients had electrocardiographic (ECG) voltage evidence of LVH, and three of these had the left ventricular “strain” pattern. It had been planned initially to include only patients with posterior wall thickness of 1.1 cm or more, but of the 12 patients who completed the study, two had posterior wall thickness of less than 1.1 cm.

Study design. All patients had documented essential hypertension with a supine diastolic pressure of equal to or greater than 90 mm Hg but equal to or less than 155 mm Hg on at least three occasions over a 2 week period while receiving no medication. Therapy with atenolol was then commenced with a single daily 100 mg dose. An adequate response to this medication was considered to be present if the supine diastolic pressure fell to less than 90 mm Hg. If blood pressure did not fall to less than 90...
mm Hg after 4 weeks of atenolol therapy then a diuretic was added. If this combination failed to control pressure then the patient was withdrawn from the study. After entry into the study, all patients underwent a complete history and physical examination, a full biochemical panel, 12 lead electrocardiography, chest x-ray, and M Mode echocardiography. The patients were then given a single 100 mg atenolol tablet and the echocardiographic examination was repeated 12 hr later. Further echocardiograms were obtained after 1 week, 1 month, 3 months, 6 months, 9 months and 1 year. Electrocardiograms were obtained at the same intervals throughout the study (except at 12 hr).

**Electrocardiography.** The electrocardiograms were performed in a standard manner; voltages were measured without knowledge of the time during the study when the electrocardiograms were obtained. Voltage measurements of ECG changes were made with both the sum of the S wave in V1 and that of the R wave in V4 and also the deepest precordial S wave and tallest precordial R wave. ECG LVH was calculated by both the Sokolow-Lyon13 and the Romhilt-Estes criteria.14 In addition, analysis of the ST segment and T waves were made at each stage during the study.

**Echocardiography.** All echocardiograms were obtained with a Smith Kline M mode 20A Ultrasonicoscope; only patients with technically acceptable echocardiograms were included in the study. The techniques for visualization of the left ventricle have been described in detail,14 and previously validated methods were used to reduce the errors associated with the method to a minimum.15 Measurements were made of posterior wall thickness, septal wall thickness, systolic dimension, and diastolic dimension. From these data fractional fiber shortening, ejection fraction, and left ventricular mass were derived. Left ventricular mass was calculated based on the formula 1.05 (LVID + IVS + LVPW)3, as described by Devereux,16 but by use of the standard leading edge to leading edge.17 All echocardiograms were read by two individuals without knowledge of the time during the study that the echocardiogram was recorded.

**Statistics.** Analysis of variance was applied to the data followed by use of the least square means to determine which visit differed markedly from baseline.18 Baseline values in all cases were defined as the last observations before initiation of atenolol treatment.

**Results**

Twelve of the fifteen patients who were enrolled in the trial completed the study. Of the three excluded patients, one failed to return after 8 months of therapy, one had insomnia and impotence thought possibly to be drug-related, and one developed hives, itching, facial swelling, and dizziness 1 hr after the first dose. Five of the remaining 12 patients required the addition of diuretic therapy to produce the required fall in blood pressure, as specified by the protocol. All five were black, thus confirming previous data on the reduced responsiveness of black patients to β-adrenoreceptor-blocking agents.19

Outpatient supine systolic and diastolic pressures fell from 155 ± 3 and 99 ± 1 to 131 ± 3 and 83 ± 2 mm Hg, respectively (p < .001). These reductions of all three indexes were detected as early as 12 hr after administration of the first atenolol tablet, and remained significantly diminished at every stage during the study (table 1). Standing systolic and diastolic pressures were also reduced significantly from 148 ± 2/102 ± 1 to 126 ± 3/87 ± 2 mm Hg (table 1) without evidence of postural hypotension. Standing pulse rate was reduced from 81 ± 2 to 63 ± 3 beats/min.

Electrocardiographic evidence of LVH was present in six and eight patients by the Romhilt-Estes and Sokolow-Lyon criteria, respectively; three of the latter eight patients had ST-T wave changes in left ventricular strain. By both criteria, only two patients had LVH at the end of the study, with this difference reaching significance for Sokolow-Lyon criteria by chi-square analysis (p < .05); (table 2). In the three patients with the ST-T wave changes, the LVH strain pattern had resolved after 6 months. In terms of actual voltage measurements, a reduction in voltages was evident at 6 months (p < .05) by the criteria of the deepest precordial S wave and tallest R waves, and by 12 months by the S wave in V1 and R wave in V5 criteria (table 3). According to echocardiographic measurements, posterior and septal wall thicknesses became significantly reduced after 1 month of therapy. The posterior wall thickness was decreased from 1.16 ± 0.03 to 1.08 ± 0.03 cm (p < .05), and septal thickness was

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 hr</th>
<th>1 week</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>1 year</th>
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<tbody>
<tr>
<td><strong>Supine</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>155 ± 3</td>
<td>148 ± 8*</td>
<td>140 ± 5*</td>
<td>140 ± 4*</td>
<td>131 ± 4*</td>
<td>128 ± 4*</td>
<td>136 ± 5*</td>
<td>131 ± 3</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>99 ± 1</td>
<td>88 ± 4*</td>
<td>88 ± 3*</td>
<td>88 ± 2*</td>
<td>88 ± 2*</td>
<td>85 ± 2*</td>
<td>85 ± 2*</td>
<td>83 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 ± 2</td>
<td>60 ± 3*</td>
<td>61 ± 3*</td>
<td>55 ± 2*</td>
<td>57 ± 2*</td>
<td>55 ± 3*</td>
<td>59 ± 3*</td>
<td>51 ± 3</td>
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<tr>
<td><strong>Standing</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>148 ± 2</td>
<td>126 ± 3*</td>
<td>131 ± 5*</td>
<td>138 ± 4*</td>
<td>131 ± 4*</td>
<td>127 ± 4*</td>
<td>127 ± 4*</td>
<td>126 ± 3</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>102 ± 1</td>
<td>87 ± 2*</td>
<td>89 ± 3*</td>
<td>91 ± 3*</td>
<td>39 ± 2*</td>
<td>85 ± 1*</td>
<td>88 ± 2*</td>
<td>87 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81 ± 2</td>
<td>63 ± 3*</td>
<td>67 ± 4*</td>
<td>59 ± 2*</td>
<td>62 ± 2*</td>
<td>60 ± 3*</td>
<td>65 ± 3*</td>
<td>64 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*Ap < .01.
TABLE 2
Number of patients with ECG evidence of LVH at different stages during the study

<table>
<thead>
<tr>
<th>ECG LVH</th>
<th>Normal</th>
<th>Estes-Romhilt criteria</th>
<th>Sokolow-Lyon criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>1 month</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>3 months</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6 months</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>9 months</td>
<td>9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>12 months</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*p < .05 (chi square).

reduced from 1.28 ± 0.07 to 1.19 ± 0.05 cm (p < .05). This reduction was maintained for the duration of the study (table 4). The final posterior and septal wall thicknesses were 1.06 ± 0.02 and 1.18 ± 0.04 cm, respectively. Diastolic dimension was increased significantly only after 1 month (p < .05); but the systolic and diastolic dimensions were no different from baseline measurements at all other times. Although left ventricular mass index only became significantly reduced at the sixth month, it remained significantly more reduced at the twelfth month (table 4). Thus, reductions in left ventricular mass and ECG voltage followed a similar time course, whereas changes in left ventricular wall thickness were detected earlier (figure 1). Left ventricular function, as assessed by both ejection fraction and fractional fiber shortening rate, remained unchanged throughout the study (table 4).

Discussion

Echocardiography is now firmly established as an accepted method for assessing the degree of cardiac involvement in hypertension as well as for the serial assessment of the effects of antihypertensive therapy on left ventricular wall thickness, mass, and function. In this regard, echocardiography has been most useful in demonstrating changes in left ventricular wall thicknesses and mass with antihypertensive agents both singly and in combination. Thus, adrenergic inhibitors, converting-enzyme inhibitors, and β-adrenoreceptor–blocking agents have all shown to diminish left ventricular wall thicknesses and mass. More recently, we have shown a reduction in left ventricular mass with the calcium slow-channel blocker diltiazem, and others have demonstrated similar findings with nifedipine. In contrast, these changes have not been seen with thiazide diuretics in man or with the direct-acting vasodilators in experimental animal studies. Since the purpose of this study was to assess the time course of regression of LVH, we believed it important to choose a drug that did not require titration, promptly reduced arterial pressure as monotherapy in the majority of patients, and had been shown previously to cause regression of LVH. Atenolol most closely fitted these prerequisites and was therefore selected. Since the thiazide diuretics do not produce these changes in and of themselves, these agents were considered to be a suitable additional agent should pressure not be controlled optimally with atenolol alone.

Atenolol was indeed an effective antihypertensive drug, producing a highly significant reduction in arterial pressure and in heart rate. These changes were demonstrated as early as 12 hr after initiation of therapy. Blood pressure control was satisfactory in seven patients; the remaining five patients required the addition of a thiazide diuretic. It was of interest that each of these five patients was black, thus confirming previous reports of a suboptimal response of black patients to β-blocking therapy but a better response to thiazide diuretics. Reduction in blood pressure was satisfactorily maintained throughout the study, and there was a further fall in pressure at the 12 month review. Thus, this medication program was well tolerated by all patients who completed this study.

A possible weakness of study regards the lack of control data, but in view of the fact that we were following hypertensive patients with LVH we did not believe that it was feasible to follow a similar group of patients without intervention. In a previous study of the effect of antihypertensive therapy in patients with hypertension, we demonstrated that in patients without LVH at the outset very constant measurements were obtained before and after a prolonged period of blood pressure control. This, coupled with our earlier reproducibility study, would support the view that the serial changes seen in this study genuinely reflected

TABLE 3
ECG voltage changes with atenolol

<table>
<thead>
<tr>
<th></th>
<th>SV&lt;sub&gt;1&lt;/sub&gt; + RV&lt;sub&gt;5&lt;/sub&gt;</th>
<th>SD + R&lt;sub&gt;T&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>34.7 ± 7.6</td>
<td>38.5 ± 6.4</td>
</tr>
<tr>
<td>1 month</td>
<td>32.6 ± 8.4</td>
<td>37.3 ± 7.2</td>
</tr>
<tr>
<td>6 months</td>
<td>31.0 ± 7.9</td>
<td>33.6 ± 3.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 year</td>
<td>28.9 ± 7.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.8 ± 6.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

SV<sub>1</sub> + RV<sub>5</sub> = the sum of the S wave in V<sub>1</sub> and R wave in V<sub>5</sub>;

SD + R<sub>T</sub> = the sum of the deepest S wave and the tallest R wave in the precordial leads.

<sup>a</sup>p < .05; <sup>b</sup>p < .01.
TABLE 4
Echocardiographic indexes at baseline and at various intervals during therapy with atenolol

<table>
<thead>
<tr>
<th>Index</th>
<th>Baseline</th>
<th>12 hr</th>
<th>1 week</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>1.16±0.03</td>
<td>1.14±0.02</td>
<td>1.10±0.04</td>
<td>1.08±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.08±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.09±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.07±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.06±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Septal thickness (cm)</td>
<td>1.28±0.07</td>
<td>1.25±0.05</td>
<td>1.26±0.07</td>
<td>1.19±0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.21±0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.19±0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.20±0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.18±0.06&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic dimension (cm)</td>
<td>4.75±0.13</td>
<td>4.75±0.22</td>
<td>4.90±0.19</td>
<td>5.07±0.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.92±0.23</td>
<td>4.61±0.17</td>
<td>4.89±0.2</td>
<td>4.76±0.2</td>
</tr>
<tr>
<td>Systolic dimension (cm)</td>
<td>3.02±0.13</td>
<td>3.00±0.19</td>
<td>3.10±0.13</td>
<td>3.10±0.20</td>
<td>3.09±0.23</td>
<td>2.85±0.17</td>
<td>2.94±0.12</td>
<td>2.92±0.1</td>
</tr>
<tr>
<td>LV mass index (g/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.44±9</td>
<td>1.44±10</td>
<td>1.46±11</td>
<td>1.44±7</td>
<td>1.38±8</td>
<td>1.25±6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.37±10</td>
<td>1.27±7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fractional fiber shortening (%)</td>
<td>36±2</td>
<td>36±2</td>
<td>38±2</td>
<td>38±2</td>
<td>37±2</td>
<td>38±1</td>
<td>39±1.2</td>
<td>38±2</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>65±2</td>
<td>65±3</td>
<td>67±2</td>
<td>68±2</td>
<td>66±2</td>
<td>68±1</td>
<td>69±2</td>
<td>68±2</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
LV = left ventricular.
<sup>a</sup>P < .05; <sup>b</sup>P < .01.

alterations in left ventricular wall thicknesses and mass and were not occurring independently of the intervention.15

Our findings of significantly diminished posterior and septal wall thicknesses and left ventricular mass after atenolol confirm previous reports.7-9, 24 However, these studies were not concerned with the time when regression of the ECG and echocardiographic changes associated with LVH occurs. In one study, no changes in wall thicknesses were detected 1 month after commencing therapy with atenolol, although significant reductions in wall thicknesses and left ventricular mass were noted after 1 year. Other studies involving only one echocardiographic measurement made during treatment revealed reduced left ventricular wall thickness and mass at 2<sup>4</sup> and 5 months, respectively.7 In the present study we chose to obtain a total of seven echocardiographic recordings over a period of 1 year to determine at which point a significant reduction in left ventricular wall thicknesses occurred. Our findings were of particular interest in demonstrating that wall thickness changes were seen as early as 1 month after institution of therapy, although changes in left ventricular mass did not occur until 6 months after commencement of therapy. Significant ECG changes were noted at the same time that left ventricular mass decreased, but these changes took place after the decreases in wall thicknesses were observed. This may

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**FIGURE 1.** Time course of changes in systolic pressure, diastolic pressure, posterior wall thickness, and left ventricular mass before and during atenolol therapy.
be partly explained by the finding that ECG voltage changes seem to reflect not only wall thickness but also intraventricular cavity size. Therefore, these voltage changes might be expected to follow changes in mass more closely than wall thickness changes. Indeed, it was the increment in diastolic dimension at 1 month that was the main contributing factor to the finding that left ventricular mass did not change at this time.

Furthermore, this factor is also likely to have affected the ECG voltage changes at 1 month. Therefore, this study has demonstrated that the echocardiographic changes that take place after institution of antihypertensive therapy can be maintained with prolonged control of blood pressure without any deterioration of resting left ventricular function. In addition, those patients demonstrating the greatest fall in arterial pressure did not necessarily have the greatest reduction in wall thickness and mass. This is not surprising since it is now well-established that a number of factors in addition to the blood pressure level influence the degree of LVH.

In conclusion, the time course of regression of ventricular hypertrophy has been demonstrated in this study with the use of a single daily dose of atenolol. Significant reductions in septal and posterior wall thicknesses occur as early as 4 weeks after initiation of therapy, while alterations in left ventricular mass and ECG voltages are seen at a later stage. Regression of LVH was maintained throughout the year-long period of the study without any adverse effects to resting left ventricular function.

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