Effect of Atenolol on Left Ventricular Function in Hypertensive Patients

M. Mohsen Ibrahim, M.B., B.Ch., M.D., M. Aziz Madkour, M.B., B.Ch.,
and Ragaa Mossallam, M.B., B.Ch., D.M.

SUMMARY No information is available about the effects of oral atenolol, a cardioselective β-adrenergic blocking agent with no intrinsic sympathomimetic activity, on left ventricular function. Atenolol, 100 mg/day, was given to 12 hypertensive patients for 8 weeks, and its effects on mean arterial pressure (MAP), cardiac index (CI) and ejection phase indexes of myocardial performance were examined by echocardiography. Echocardiographic studies were performed before treatment, after 4 weeks of placebo, and repeated after 4 and 8 weeks of atenolol therapy. MAP fell by 14% and 21% after 4 and 8 weeks, respectively. CI fell by 22% and 20% and stroke index (SI) fell by 11% and 7%. Calculated peripheral resistance did not change significantly. Fractional shortening, ejection fraction and normalized mean rate of circumferential fiber shortening did not change. The normalized mean posterior wall velocity decreased after 4 weeks but returned to pretreatment levels after 8 weeks. The septal velocity increased after 8 weeks. End-diastolic volume index (EDVI) did not change, and there was no relationship between changes in heart rate and EDVI.

The study shows that atenolol in the resting state has no effect on certain echocardiographic indexes of left ventricular (LV) function when given orally to hypertensive patients with normal LV size and function. The reduction in CI and SI were presumably secondary to a decrease in cardiac venous filling.

ATENOLOL is a new β-adrenergic receptor blocking drug with cardioselective properties that has no intrinsic sympathomimetic action or membrane-stabilizing activity. It is effective in the treatment of hypertension. In acute and long-term hemodynamic studies, atenolol produced a marked reduction in cardiac output (CO), with variable or little effect on calculated total peripheral resistance (TPR). Studies in animals have shown that atenolol has no negative inotropic effect. However, the effects of atenolol on myocardial contractility have been demonstrated less often in man and only in acute i.v. experiments. Information regarding its effect on left ventricular (LV) function after oral therapy have not been reported. Previous studies with β-adrenergic blocking drugs have shown lack of similarity in hemodynamic response between i.v. and long-term oral administration.

We studied the effects of oral atenolol therapy on arterial pressure, CO and LV contractile state in hypertensive patients.

Echocardiography was used in this study to measure LV dimensions and to assess LV function. Good correlation between angiographic and echocardiographic measurements of LV dimensions and indexes of myocardial contractility has already been demonstrated.

Methods

Twelve male patients with essential hypertension were studied on an outpatient basis. Secondary hypertension was excluded by the usual routine procedures. All patients were asked to participate in the study voluntarily. They gave formal consent after a detailed explanation of the aims and objectives of investigation. Table 1 shows the clinical characteristics of the patients. Patients were excluded if they had severe sinus bradycardia, more than grade I aortic stenotic block, congestive heart failure, bronchial asthma, uncontrolled diabetes mellitus, valvular heart disease, clinical and/or electrocardiographic evidence of coronary artery disease or radiologic evidence of cardiac enlargement, or if they were markedly obese or had severe chest deformity that made adequate echocardiographic examination impossible. Patients with malignant or accelerated hypertension (grade IV and III retinopathy) were also excluded.

Study Design

Each patient was followed initially for 4 weeks. All previous antihypertensive medication was discontinued and placebo was given. Blood pressure and heart rate (HR) were checked twice weekly in the supine and standing positions. If at the end of this 4-week placebo pretreatment period supine diastolic blood pressure was greater than 95 mm Hg, the patient was included in the study. Only patients with very good, readable echocardiographic recordings were studied. Patients with poor records were excluded. During a further 4-8-week treatment period, all patients were started on a dose of 100 mg of atenolol daily.

Echocardiographic Studies

At the conclusion of the 4-week pretreatment (first placebo) period, each patient underwent echocardiographic evaluation as described previously. These studies were performed under standard conditions in the morning, at the same hour of the day (9–10:30...
a.m.) after an overnight fast. Studies were made in a quiet room where lights were dimmed and minimal disturbance was allowed. The safety and the noninvasive nature of the procedure were explained to the patient. Each patient remained resting supine for 30 minutes before the start of echocardiographic examination. The head part of the examination table was elevated 30° above horizontal. During recording, the patient’s head and shoulders were elevated while he was lying in the left lateral position with his left arm turned up toward his head. This position was reproducible because the angle of elevation and the degree of left lateral rotation were constant.

The echocardiograms were recorded with a Unirad ultrasonoscope model 489 Sono III-GZD using a 2.25-MHz transducer with an active diameter of 13 mm and internal focus 4–7 cm, with a repetition rate of 1000 impulses/sec. The ultrasonoscope was coupled to a strip-chart recorder. Recordings were obtained at paper speed of 50 mm/sec and, when necessary, 100 mm/sec. Each patient had an ECG recorded simultaneously with the echocardiogram. Particular care was taken to standardize the pathway of the ultrasonic beam through the left ventricle, to correctly identify the internal and external surfaces of the LV walls. Measurements of LV dimensions were made at an angle in which fragmental echoes of the mitral valve were seen. The interventricular septum and posterior wall endocardial echoes could then be recorded at the level of the chordae (fig. 1). Patients were asked to breath quietly during recording. Inconsistency in placement and technique of handling the echocardiographic transducer were avoided by keeping a record for each patient indicating the transducer position selected at the first visit. To obtain consistent and reproducible recordings, the standard intercostal space technique was used. The transducer was held perpendicular to the chest wall, with only slight medial or lateral but no superior or inferior angulation, while permitting recording of the anterior mitral leaflet. Care was taken to reproduce the identical minor axis chord and largest ventricular dimension by scanning in the direction of both major and minor axes at each subsequent visit.

**Measurements and Calculations**

The LV echocardiographic dimensions were measured from the endocardial echo of the posterior wall to the endocardial echo of the left side of the interventricular septum. Wall and cavity measurements were made by using a leading edge method (from the anterior most edge of endocardial lines) and by using the thinnest continuous echo lines. Following the recommendations of the American Society of Echocardiography, the diameter at end-diastole (EDD) was measured at the onset of the QRS complex and diameter at end-systole (ESD) was measured at the point of the smallest distance separating the septum from the posterior wall (fig. 1). The LV ejection time (LVET) was measured from the aortic valve echoagram or from a simultaneously recorded external carotid arterial pulse tracing. Posterior LV wall excursion (PWE) was measured from the most posterior point of the LV endocardial tracing to the most anterior point in systole. Similar points at the beginning and peak of the septal systolic excursion were selected to measure septal excursio (IVSE).

Echocardiographic measurements were made directly with a millimeter ruler and calipers. The raw measurements were multiplied or divided by a conversion factor that expressed how many real millimeters a 1-cm standard occupies on the echocardiogram.

LV volumes were derived by cubing EDD and ESD. The difference between the end-diastolic volume...
The normalized mean rate of circumferential fiber shortening (Vcf) (circ/sec) was calculated as

$$\frac{EDD - ESD}{LVET \times EDD}.$$  

The normalized mean posterior wall velocity (Vpw) (sec') was calculated as

$$\frac{PWE}{LVET \times EDD}.$$  

Similarly, the normalized mean interventricular septal velocity (Vivs) (sec') was calculated as

$$\frac{IVSE}{LVET \times EDD}.$$  

All calculations were made using the average obtained from eight cardiac cycles.

Echocardiographic measurements were determined independently by two of the investigators and the results were compared. Only twice were measurements not consistent, and in both cases the echocardiographic records were reexamined by both investigators. One investigator had difficulty defining the LV posterior wall endocardium.

Blood pressure was recorded immediately before each study by two observers with a standard sphygmomanometer cuff. The mean of three blood pressure readings (same arm) after 30 minutes of supine rest was recorded. Diastolic blood pressure was measured at phase V Korotkoff sounds. The mean arterial pressure (MAP) was calculated by adding one-third the pulse pressure to the diastolic blood pressure (DBP):

$$MAP = DBP + \left(\frac{SBP - DBP}{3}\right)$$

where SBP = systolic blood pressure.

Corrections were made to account for changes in body surface area (BSA). The cardiac index (CI), stroke index (SI) and the end-diastolic volume index (EDVI) were obtained by dividing the CO, SV and EDV by the BSA, respectively. The CI and calculated mean blood pressure were used to estimate the total peripheral resistance. The TPR was determined indirectly and was derived from the equation:

$$TPR.m^2 (Us) = \frac{MAP}{CI}$$

Echocardiographic studies were repeated in all patients after 4 weeks of atenolol treatment and again for the third time after 8 weeks in eight patients.

Reproducibility Studies

The reproducibility of echocardiographic measurements was examined in seven healthy, normotensive
volunteers. Serial echocardiographic recordings were made under the previous standard conditions and with the same precautions. Measurements were repeated after 6 weeks. Calculations of averages, paired t tests, analysis of variance, correlation coefficients, and statistical significance of results were performed by standard methods.24 The threshold of significance was \( p < 0.05 \).

Results

The results of the present study are shown in tables 2 and 3 and in figures 2–10.

Arterial Pressure

The blood pressure was reduced in all subjects by 10% or more. The pretreatment MAP was 141 ± 4.79 mm Hg (mean ± SEM) (range 115–170 mm Hg). At the conclusion of 4 weeks of atenolol treatment (100 mg/day), MAP fell to 121 ± 4.72 mm Hg (range 101–155 mm Hg), a 14% reduction. After 8 weeks of therapy MAP fell by 30 ± 2.41 mm Hg, 21% from the pretreatment level (table 2 and fig. 2).

Heart Rate

HR decreased in all patients. The pretreatment rate

Figure 2. Changes in mean arterial pressure and total peripheral resistance after 4 and 8 weeks of atenolol treatment. Bars represent the SEM.

Figure 3. Changes in stroke index and cardiac index after 4 and 8 weeks of atenolol (A) treatment. C = control (pretreatment measurements).

Figure 4. Degree of reduction in cardiac index and stroke index after 4 and 8 weeks of atenolol treatment. Bars represent SEM.
Table 2. Effects of Atenolol on Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>CI (l/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>141</td>
<td>121</td>
<td>114</td>
</tr>
<tr>
<td>SD</td>
<td>15.9</td>
<td>15.67</td>
<td>16.49</td>
</tr>
<tr>
<td>SE</td>
<td>4.79</td>
<td>4.72</td>
<td>6.23</td>
</tr>
<tr>
<td>p C vs 1</td>
<td>&lt; 0.001</td>
<td>NS</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>p C vs 2</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
<td>&lt; 0.010</td>
</tr>
<tr>
<td>p 1 vs 2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; SI = stroke index; TPR = total peripheral resistance; LVET = left ventricular ejection time; C = control measurements after 4 weeks of placebo; 1 = atenolol therapy for 4 weeks; 2 = atenolol therapy for 8 weeks.

Table 3. Effects of Atenolol on Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>EDVI (ml/m²)</th>
<th>FS (%)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>93</td>
<td>95</td>
<td>78</td>
</tr>
<tr>
<td>SD</td>
<td>19.57</td>
<td>23.93</td>
<td>17.46</td>
</tr>
<tr>
<td>SE</td>
<td>5.90</td>
<td>7.22</td>
<td>6.60</td>
</tr>
<tr>
<td>p C vs 1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p C vs 2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p 1 vs 2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: EDVI = end-diastolic volume index; FS = fractional shortening; EF = ejection fraction; Vcf = normalized mean rate of circumferential fiber shortening; Vpw = normalized mean posterior wall velocity; AVCF = normalized mean interventricular septal velocity; C = control measurements after 4 weeks of placebo; 1 = atenolol therapy for 4 weeks; 2 = atenolol therapy for 8 weeks.

Figure 5. Relationship of changes in velocity of circumferential fiber shortening (Vcf) and the fall in cardiac index (CI) (r = 0.726, p < 0.01). Patient 2 was not included. Measurements of Vcf were not available in all patients because precise measurements of left ventricular ejection time were difficult in some patients.

Treatment CI fell (fig. 3) to 3.57 ± 0.30 l/min/m² (range 0.22-2.60 l/min/m²), a 22% decrease (fig. 4). The fall in CI was maintained at the eighth week of therapy; it was 3.30 ± 0.21 l/min/m², a 20% decrease from initial control readings. CI fell from the pretreatment level in all patients except one, who had an increase of 0.65 l/min/m². On the other hand, comparison with 4-week measurements showed an increase of CI in six patients and decrease in two (fig. 3). There was no relationship between changes in CI and changes in MAP, but the changes were significantly

Cardiac Index

The pretreatment CI was 4.58 ± 0.28 l/min/m²* (range 3.15-5.95 l/min/m²). After 4 weeks of atenolol treatment CI fell (fig. 3) to 3.57 ± 0.30 l/min/m² (range 0.22-2.60 l/min/m²), a 22% decrease (fig. 4). The fall in CI was maintained at the eighth week of therapy; it was 3.30 ± 0.21 l/min/m², a 20% decrease from initial control readings. CI fell from the pretreatment level in all patients except one, who had an increase of 0.65 l/min/m². On the other hand, comparison with 4-week measurements showed an increase of CI in six patients and decrease in two (fig. 3). There was no relationship between changes in CI and changes in MAP, but the changes were significantly

*The range of cardiac index in normal subjects for our laboratory is 3.56-5.47 l/min/m² using echocardiographic methods.

Figure 6. Relationship between changes in velocity of circumferential fiber shortening (Vcf) and changes in stroke index (SI) (r = 0.694, p < 0.01). Patient 2 was not included.
related to changes in Vcf \((r = 0.726, p < 0.01)\) (fig. 5). Patient 2 was not included.

**Stroke Index**

The pretreatment SI ranged between 45 and 95 ml/m² \((66 \pm 4.87 \text{ ml/m}^2)\). Changes after atenolol treatment were variable and inconsistent (fig. 3). At the conclusion of 4 weeks of therapy SI increased in four patients and decreased in eight. It decreased an average of 7.3 ml/m², or 11%. After 8 weeks SI fell by 4.5 ml, or 7%, from the pretreatment level (fig. 4). It increased in four patients and it decreased in four (fig. 3). Compared with the 4-week readings, SI increased in five patients and decreased in three.

There was significant correlation between changes in SI and changes in Vcf \((r = 0.694, p < 0.01)\) (fig. 6); patient 2 was not included in this analysis. The fall in MAP was not related to changes in SI (fig. 7). Other factors influencing cardiac function remained constant. A fall in MAP is expected to result in better LV ejection and a larger SI.

**Total Peripheral Resistance**

The pretreatment TPR index (TPRI) was 22–50 units/m² \((33 \pm 2.87 \text{ units/m}^2)\). After 4 weeks of atenolol treatment, the changes were inconsistent and variable. TPRI increased in seven patients, decreased in four and did not change in one. The net result was an increase by 4.08 ± 2.16 units/m², or 12% (fig. 2). After 8 weeks the TPRI increased in four patients and decreased in the other four. The result was a decrease of 1.13 ± 3.25 units/m², or 3% (fig. 2). The very large standard error of the mean made these changes insignificant.

**Ejection Time**

The LVET increased after 4 and 8 weeks of therapy (table 2), but the changes were not statistically significant.
End-diastolic Volume Index (EDVI)

The pretreatment EDVI ranged from 63–129 ml/m² (93 ± 5.9 ml/m²). At the conclusion of 4 weeks treatment the changes were insignificant and inconsistent. EDVI decreased in seven patients, did not change in three and it increased in two. Similarly, after 8 weeks no significant or consistent changes were found (fig. 8, table 3). Changes in HR and EDVI were not related (fig. 9).

Fractional Shortening

Changes in FS were insignificant after both 4 and 8 weeks of therapy. The pretreatment FS ranged between 22–49% (34.9 ± 2.16%). After atenolol treatment (4 weeks), FS decreased in six patients, increased in five and did not change in one, and it ranged between 25–44% (33.8 ± 1.66%). After 8 weeks changes were also inconsistent and insignificant. FS increased in five patients and decreased in three; the mean value was 35.3 ± 2.74% (table 3).

Ejection Fraction

EF did not change after atenolol treatment (table 3). The pretreatment values ranged between 0.52–0.86 (0.71 ± 0.028). Figure 8 shows the variable and inconsistent changes in EF after 4 and 8 weeks of atenolol therapy.

FIGURE 8. Changes in ejection fraction and end-diastolic volume index in a patient after 4 and 8 weeks of atenolol (A) treatment. C = control (pretreatment measurements).

FIGURE 9. Relation between heart rate and end-diastolic volume index (EDVI) in every patient before and after atenolol therapy. No correlation was present. Arrows point to the direction of change from the control pretreatment level to measurements after atenolol treatment. Changes in heart rate produced no uniform pattern of change in EDVI.

FIGURE 10. Changes in velocity of circumferential fiber shortening (Vcf) in each patient after 4 and 8 weeks of atenolol (A) treatment. Changes were inconsistent and insignificant. C = control (pretreatment measurements).
Normalized Mean Vcf

Changes in Vcf after atenolol therapy were insignificant. The pretreatment values ranged from 0.52–1.60 circ/sec (1.13 ± 0.088 circ/sec). After 4 weeks of atenolol Vcf decreased by 0.12 ± 0.08 circ/sec, it decreased in eight patients and increased in three, and the average was 1.05 ± 0.078 circ/sec (fig. 10). Measurements of Vcf were not available in all patients because it was sometimes difficult to get precise measurements of LVET. After 8 weeks Vcf was 1.19 ± 0.14 circ/sec. It decreased from pretreatment rates in three patients and increased in two (fig. 10). Changes were not significant after either 4 or 8 weeks of treatment.

There was a positive correlation between the changes in Vcf and the changes in CI and SI (figs. 5 and 6), as stated previously. However, the fall in MAP and the changes in Vcf were not related.

Normalized Mean Posterior Wall Velocity (Vpw)

The Vpw decreased at the completion of 4 weeks of atenolol treatment; however, after 8 weeks it increased to the pretreatment level (table 3). The pretreatment Vpw varied between 0.52–1.0 sec⁻¹ (0.82 ± 0.04 sec⁻¹). After 4 weeks it decreased in nine patients, did not change in one and increased in one (range 0.52–0.89 sec⁻¹). After 8 weeks, Vpw decreased from pretreatment levels in three patients and increased in two (range 0.60–1.1 sec⁻¹).

Normalized Mean Interventricular Septal Velocity (Vivs)

There was no significant change in Vivs after 4 weeks of atenolol treatment, but it increased at the end of the eighth week (table 3). The pretreatment Vivs varied between 0.30–0.91 sec⁻¹. After 4 weeks it increased in seven patients and decreased in four (range 0.37–0.73 sec⁻¹). After 8 weeks the Vivs increased in four patients and decreased in one (range 0.37–0.70 sec⁻¹).

Reproducibility

Table 4 shows changes in EDD, ESD, HR and CI 6 weeks apart in seven healthy, normotensive subjects. Difference in CI ranged from 1–15% (mean 6.9%).

To measure the accuracy of the method, a “homogeneity test” was done to the readings and was not significant.

The average difference between successive readings (temporal variation) was calculated and tested by the paired t test and was not significant. The temporal variation and interobserver variation were tested together by the analysis of variance “ANOVAR method” (two factors). Neither factor was statistically significant.

Discussion

Studies of LV function in hypertensive patients have been hampered because of the difficulty in conducting direct intraventricular studies in asymptomatic patients. When such studies are available, results have been questionable because the hemodynamic status may have been altered by premedication or the associated anxiety of the procedure. Echocardiography is noninvasive and a relatively simple and accurate method for measurements of cardiac dimensions and assessment of LV function. Studies at cardiac catheterization with LV angiography repeatedly confirmed the good correlation between echocardiographic and angiographic measurements in

<table>
<thead>
<tr>
<th>Case</th>
<th>EDD₁ (cm)</th>
<th>EDD₂ (cm)</th>
<th>ESD₁ (cm)</th>
<th>ESD₂ (cm)</th>
<th>HR₁ (beats/min)</th>
<th>HR₂ (beats/min)</th>
<th>CI₁ (ml/min/m²)</th>
<th>CI₂ (ml/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.7</td>
<td>4.8</td>
<td>3.1</td>
<td>3.2</td>
<td>70</td>
<td>72</td>
<td>2658</td>
<td>2873</td>
</tr>
<tr>
<td>2</td>
<td>4.7</td>
<td>4.6</td>
<td>3.3</td>
<td>3.0</td>
<td>80</td>
<td>72</td>
<td>3158</td>
<td>2944</td>
</tr>
<tr>
<td>3</td>
<td>5.3</td>
<td>5.2</td>
<td>3.6</td>
<td>3.2</td>
<td>65</td>
<td>65</td>
<td>4232</td>
<td>4464</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>5.2</td>
<td>3.1</td>
<td>3.8</td>
<td>92</td>
<td>92</td>
<td>4976</td>
<td>4481</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>5.3</td>
<td>3.4</td>
<td>4.0</td>
<td>92</td>
<td>92</td>
<td>4749</td>
<td>4704</td>
</tr>
<tr>
<td>6</td>
<td>5.2</td>
<td>5.4</td>
<td>3.4</td>
<td>3.8</td>
<td>88</td>
<td>74</td>
<td>4980</td>
<td>4241</td>
</tr>
<tr>
<td>7</td>
<td>5.3</td>
<td>5.2</td>
<td>3.3</td>
<td>3.6</td>
<td>75</td>
<td>92</td>
<td>4916</td>
<td>5025</td>
</tr>
<tr>
<td>Mean</td>
<td>5.03</td>
<td>5.10</td>
<td>3.31</td>
<td>3.51</td>
<td>80</td>
<td>80</td>
<td>4238</td>
<td>4104</td>
</tr>
<tr>
<td>SEM</td>
<td>0.11</td>
<td>0.12</td>
<td>0.07</td>
<td>0.16</td>
<td>4.41</td>
<td>4.78</td>
<td>390</td>
<td>348</td>
</tr>
</tbody>
</table>

Mean difference -0.07  -0.20  134
SAD  0.06  0.15  151
t  1.20  1.35  0.96

Abbreviations: EDD₁ = end-diastolic diameter; ESD₁ = end-systolic diameter; HR = heart rate; CI = cardiac index; 1 and 2 refer to the initial and the second serial measurements after 6 weeks; SEM = standard error of the mean; SAD = standard error of the difference.
patients without LV asynergy. Because only small segments of the interventricular septum and posterior wall of the left ventricle are studied with standard time-motion echocardiography, an important assumption in calculating LV volumes is that the pattern of LV contraction is uniform and symmetric. We excluded patients with clinical or electrocardiographic evidence of coronary artery disease, a common cause of LV asynergy. Also, we excluded patients with cardiomegaly, an important source of error in calculating LV volumes by echocardiography. To avoid the effects of phasic respiration on LV dimensions and derived LV function, patients were asked to breathe quietly during recording and the average measurement of eight consecutive cardiac cycles was taken.

The use of ejection phase indexes of myocardial performance in our study was based on data from previous observations. A linear correlation was found between echocardiographic ejection phase indexes, FS, EF, normalized mean Vcf, and similar angiographic measurements. Previous studies have shown that analysis of LV wall motion by echocardiography using the normalized velocity concept appears to be a rational and practical method for evaluating LV performance. Furthermore, ejection phase contractile indexes have been shown to provide a practical and physiologically reasonable means of assessing the level of basal myocardial contractile state, and they were found to be superior and more reliable than isovolumic indexes of myocardial performance.

Mechanism of Hypotensive Action of Atenolol

The present study supports the previously reported effectiveness of atenolol in lowering high blood pressure. All patients had a reduction in resting blood pressure of 10% or more. At the conclusion of 4 weeks of atenolol therapy MAP fell by 20 mm Hg or 14%, and after 8 weeks it fell by 30 mm Hg, or 21% from the pretreatment level. The fall in blood pressure was secondary to a reduction in CI, the effect on calculated TPR was variable and insignificant. After 8 weeks of therapy and further reduction in arterial pressure there was a tendency of TPR to decline, but changes were not significant. On the other hand, there was no correlation between the fall in MAP and the reduction in CI; thus the changes in blood pressure and CI occurred independently. The study period was too short to find whether a progressive decline in peripheral resistance is the determining factor in the hypotensive action of atenolol, similar to that reported with propranolol. However, long-term studies in subjects treated with atenolol as the sole drug for 1 year showed that the changes in TPR were inconsistent and the mean value was almost unchanged.

The reduction in CI was due to both cardiac slowing and decrease in SI. The changes in HR and SI were only significant after 8 weeks of therapy but there was no significant difference in the degree of cardiac slowing or the fall in CI at the end of the fourth and eighth weeks.

The insignificant changes in the TPR and the marked reduction in CI and HR after atenolol therapy resemble those reported by Amery et al. in a short-term study and those of Lund-Johanson in a long-term hemodynamic evaluation. However, the relative decreases in HR in these studies were more pronounced — 33% and 24%, respectively. Furthermore, changes in SI were at variance with those described by Lund-Johanson. In his studies SI was higher after therapy than before. Our findings agree with acute studies that showed a decrease or no change in SV. The difference in response to atenolol might be related to the greater degree of cardiac slowing in the Lund-Johanson observations compared with our findings. Slower HR in the presence of undisturbed venous return would allow a better filling of the heart. However, Robinson et al. found a significant fall in SV after i.v. atenolol during atrial pacing, with the HR maintained constant, and during spontaneous sinus rhythm. They concluded that the fall in CO was not purely rate-dependent.

Changes in Myocardial Contractility

Atenolol produced no significant change in the ejection phase indexes of myocardial performance. The FS, EF and Vcf did not change during atenolol therapy. The normalized mean Vpw decreased only at the initiation of therapy and returned to the pretreatment level after 8 weeks. On the other hand, the normalized mean Vvsl did not change after 4 weeks, but increased after 8 weeks. Studies in animals have shown that atenolol has no negative inotropic effect. However, acute i.v. studies in man showed a depression of isovolumic indexes of myocardial performance in both normal subjects and in patients with coronary artery disease. Ejection phase indexes were depressed significantly in coronary patients.

The EDVI did not change after atenolol treatment despite cardiac slowing. DeMaria et al. showed that in normal persons cardiac acceleration by atrial pacing produces a reduction in cardiac dimensions and an increase in Vcf and that cardiac size was significantly affected by alterations in HR. A remarkably linear relation was consistently observed between increases in HR and alterations in measurements of cardiac size.

We found no relationship between EDVI and HR (fig. 9). Atenolol might reduce cardiac venous filling, and thus, EDVI would not increase with cardiac slowing. This assumption could also explain the reduction in SI after atenolol therapy. Our studies demonstrate that atenolol given orally does not depress cardiac contractility, so reduction in SI must be due to mechanisms other than simple depression of cardiac function. Atenolol, like propranolol, could produce contraction of blood volume. Either this factor alone or a redistribution of intravascular volume away from the heart secondary to an increase in venous distensibility that favors a diminution in venous return causes the fall in SI. A decrease in venous tone after β-adrenergic blockade with pindolol.
has been reported in hypertensive patients. Although myocardial contractility plays a role in pump function, as shown by the presence of a positive correlation between changes in Vcf and changes in C1 and SI, changes in venous filling are apparently overriding. There is considerable evidence that when the contractile state of the myocardium is normal, CO is dependent more on peripheral factors and the influence these factors exert on the ventricular preload and afterload, than on the contractile state of the myocardium.

The lack of depressant effect by atenolol on myocardial contractility has significant clinical importance, because a negative inotropic effect is not welcomed in patients with cardiac insufficiency or in borderline impairment of LV function. In a previous study we gave atenolol to hypertensive patients with cardiomegaly and incipient heart failure. The drug was safe and symptoms of cardiac decompensation improved with reduction in arterial pressure in spite of β-adrenergic blockade.

The effect of β-adrenergic blocking drugs on cardiac contractility cannot be explained simply in terms of establishment of β-adrenoceptor blockade and the associated withdrawal of sympathetic support. The mechanisms whereby these drugs alter cardiac contractility are complex. Recent investigations have shown that at least some of the β-adrenoceptor antagonists interact with the plasma membrane in such a way that its capacity to store Ca++ for subsequent release is impaired and also reduce the capacity of the sarcoplasmic reticulum to accumulate Ca++ for subsequent release, hence, less Ca++ is made available for contraction. Atenolol might have a minimal effect on plasma membrane and Ca++ binding, which would explain the absence of a direct depressant effect on cardiac contractility.

In the basal resting state the sympathetic adrenergic system has minimal influence on cardiac performance; therefore, β-adrenergic blockade will influence cardiac contractility to a very small extent. Thus, in the absence of a direct cardiac depressant effect, it is not surprising that a β-adrenergic blocking drug like atenolol does not have a negative inotropic effect.

References
Possible Detection of Atherosclerotic Coronary Calcification by Two-dimensional Echocardiography

EDWIN W. ROGERS, M.D., HARVEY FEIGENBAUM, M.D., ARTHUR E. WEYMAN, M.D., ROBERT W. GODLEY, M.D., KENNETH W. JOHNSTON, AND REGINALD C. EGGLETON

SUMMARY Using two-dimensional echocardiography, a technique was developed for digitizing reflected acoustic signals and performing variable signal processing. This resulted in accentuation of differences in focal reflectivity of target tissues and improved ultrasonic tissue characterization. Study of a learning population of 200 patients demonstrated abnormal specular reflections from the proximal left coronary artery in patients with coronary artery disease. A prospective study of 100 patients was then performed to test the reliability of this method in predicting the presence of significant stenosis. Abnormal echocardiograms were a highly sensitive (94%) but less specific (65%) indicator of significant atherosclerosis of the left coronary system. One-third of patients had fluoroscopically identifiable coronary calcification, and 95% had abnormal echocardiograms. We postulate that our echocardiographic findings may be secondary to the presence of small amounts of coronary calcification. Echocardiographic tissue differentiation, therefore, may prove to be a noninvasive means of evaluating patients for coronary atherosclerosis.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY has been demonstrated to be a possible tool for examining the proximal left coronary artery. This technique has been used to describe the normal left main, left anterior descending and left circumflex coronary anatomy. In addition, decreases in coronary artery luminal diameter secondary to atherosclerotic cardiovascular disease have been visualized. Despite the desirability of noninvasively selecting patients with atherosclerotic lesions of the proximal left coronary artery, two-dimensional echocardiography has not been extensively used for this purpose because of several technical difficulties. The size of these vessels lies near the limit of resolution of echocardiography, particularly in a population of coronary patients. Variations in normal coronary anatomy are well recognized, including differences in the length of the left main coronary artery (LMCA) and the size and number of vessels present at its division. These structures move with ventricular systole relative to the ultrasonic plane. Because of the current technical limitations in directly visualizing the LMCA, we have attempted to create a technique to analyze variations in tissue properties of this region by means other than direct visualization. The goal of this research is to develop a method to accentuate the differences between sound reflected from atherosclerotic and from normal tissue. This report describes the development of such a technique. The results of an initial prospective study using this method for the identification of coronary artery disease (CAD) in a large clinical population are presented. In addition, a basis for the change in reflectivity produced by atherosclerosis is presented and the potential clinical role of this type of research discussed.

Methods To evaluate the effect of digital signal processing on the ability of echocardiography to detect changes in focal reflectivity produced by atherosclerosis, a commercially available, two-dimensional echocardiographic scanner was modified at Indiana University...
Effect of atenolol on left ventricular function in hypertensive patients.
M M Ibrahim, M A Madkour and R Mossallam

_Circulation_. 1980;62:1036-1045
doi: 10.1161/01.CIR.62.5.1036
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/62/5/1036