Short-Term Systemic Hemodynamic Adaptation to Beta-Adrenergic Inhibition with Atenolol in Hypertensive Patients

GEZA SIMON, M.D., PH.D., JOSEPH A. FRANCIOSA, M.D., HORATIO J. GIMENEZ, M.D., AND JAY N. COHN, M.D.

SUMMARY Early systemic hemodynamic adjustments to antihypertensive therapy with the cardioselective beta inhibitor, atenolol, were investigated in 12 hospitalized men, mean age 52 years, with uncomplicated mild-to-moderate essential hypertension. Twice daily measurements of cardiac output (CO) by CO3 rebreathing, blood pressure by cuff, and heart rate were performed in all subjects for 3 days before and 5 days after initiation of oral atenolol therapy (50 or 100 mg daily). Cardiac output by CO3 rebreathing was checked with dye dilution just before, and 4 hours and 4 days after the start of therapy. Plasma volume (radioiodinated albumin) was measured before therapy and on Day 5 of therapy. The CO results obtained with the two methods were not significantly different ($r = 0.88$, $p < 0.01$, $n = 12$). A reduction in heart rate, 18 ± 2 beats/min (mean ± SE), occurred in all patients while taking atenolol. By 4 hours after the first dose of atenolol, CO fell from $5.49 \pm 0.30$ to $4.24 \pm 0.21$ liters/min ($p < 0.01$), while the control mean arterial pressure (MAP) of 108 ± 4 mm Hg was not significantly changed, 110 ± 4 mm Hg. At 24 hours, CO returned near baseline (5.10 ± 0.21 liters/min) but MAP was reduced (95 ± 3 mm Hg, $p < 0.001$) and remained so thereafter. CO remained at baseline at 48 hours (5.50 ± 0.29 liters/min) but fell again ($p < 0.01$) to 4.81 ± 0.11 on Day 4 and to 4.68 ± 0.25 liters/min on Day 5 of atenolol therapy. Plasma volume, 3110 ± 100 ml before therapy, was reduced to 2850 ± 100 by Day 5 of atenolol therapy ($p < 0.01$). The findings indicate a delayed onset of the antihypertensive action of atenolol. The transient return to baseline of CO on Day 2 and 3 of atenolol therapy suggests a reverse autoregulatory adjustment to the initial fall in CO. (Hypertension 3: 262-268, 1981)

KEY WORDS • beta-adrenoceptor antagonist • atenolol • essential hypertension • systemic hemodynamics • antihypertensive therapy • cardiac output measurement

Despite extensive investigation, the mechanism of the antihypertensive action of beta-adrenoceptor inhibitors is unclear.1, 2 After parenteral or oral administration of nonselective beta inhibitors, cardiac output falls within hours but blood pressure remains unchanged.1 With the exception of one published report, the acute administration of cardioselective beta inhibitors appears to have the same hemodynamic effect.4 The antihypertensive action of beta inhibitors becomes apparent between the first and second day of drug administration.3 To understand better their mechanism of action, it would be desirable to study the systemic hemodynamic events that accompany the onset of the antihypertensive effect. Unfortunately, the constraints of invasive laboratory procedures make frequent and prolonged hemodynamic monitoring of study subjects impractical. As a result, previous studies of the systemic hemodynamic response to beta inhibitors have been performed either within hours after the first dose of the drug or several days after the initiation of therapy. In the present study, a noninvasive method was used to measure cardiac output twice daily for several days before and for 5 days after the initiation of antihypertensive therapy with the beta inhibitor, atenolol, a new cardioselective drug without sympathomimetic or membrane-stabilizing activity.7 In this manner, we were able to describe the hemodynamic sequence of events that accompanies the onset of antihypertensive action of beta inhibitors.
Methods

The subjects were 12 men, age mean 52 years, (range: 29 to 64 years), with mild or moderate hypertension. Two subjects were black, and 10 white. The average known duration of hypertension was 3 years (range: 1 to 5 years). None of the subjects had known coronary or valvular heart disease, a history of cerebrovascular disease, congestive heart failure, cardiac conduction defects, chronic obstructive lung disease, asthma, allergic rhinitis, renal insufficiency (serum creatinine greater than 1.9 mg/dl), or hypokalemia (serum potassium less than 3.8 mEq/liter, off diuretic therapy). Two patients had Grade II and three patients Grade I hypertensive retinopathy. Electrocardiographic criteria for left ventricular hypertrophy were found in only one patient. Additional diagnostic tests to rule out secondary causes of hypertension were not routinely performed in these patients. An informed consent form, in which the details of the study procedures were outlined, was signed by all subjects.

All antihypertensive medications were discontinued, and all subjects were given placebo, one tablet daily for 4 weeks. The subjects were seen weekly. Supine and standing blood pressures were checked during the weekly visits. At the end of the 4-week placebo period, the subjects were admitted to the Special Diagnostic and Treatment Unit of the Veterans Administration Medical Center, Minneapolis, for 11 days. Throughout their hospitalization, supine and standing blood pressures and heart rates of subjects were obtained in quadruplicate at 11 am, 2, 5 and 8 pm by nurses who were not acquainted with the details of the study. During the first 4 days, placebo administration of one tablet daily was continued. On Days 5 through 9, the subjects were randomly assigned in a single-blind fashion to receive either a 50 or 100 mg tablet of atenolol daily. During the last 2 days of hospitalization, placebo administration was reinstated. Placebos and medications were given in the morning at 10 am. During hospitalization, the subjects were fully ambulatory and, in their free time, were allowed to leave the ward. They chose their own diet from a daily menu without salt restriction. Body weights were checked daily.

Noninvasive Systemic Hemodynamic Measurements

On Day 1, the subjects were acquainted with the use of the apparatus for measuring cardiac output by the CO₂ rebreathing method. On Days 2 through 9, simultaneous supine heart rates, blood pressures by cuff, and cardiac outputs by the CO₂ rebreathing method were measured in duplicate twice daily, at 9:30 am and 2:00 pm, in all subjects after a 10-minute period of supine rest. The CO₂ rebreathing method for measuring cardiac output in our laboratories has been validated and described previously.⁸ Expired air was collected for 5 to 7 minutes and passed through a Parkinson Cowan dry gas meter and a Beckman LB-2 CO₂ analyzer, whose outputs of expired air volume and average CO₂ concentration were displayed on a Beckman RR-2 recorder. Arterial CO₂ was estimated by having the patient perform a slightly forced expiration at the end of a normal tidal inspiration, while the CO₂ analyzer made a breath-by-breath analysis. Mixed venous CO₂ was determined by the Collier method using a mixture of 9% CO₂ and 91% O₂. Cardiac output (liter/min) was calculated by the Fick equation. Mean arterial pressure (mm Hg) was calculated as the sum of the diastolic pressure plus one third pulse pressure. Total peripheral resistance (mm Hg/liter min⁻¹) was calculated as the ratio of mean arterial pressure and cardiac output.

Invasive Systemic Hemodynamic Measurements

On Day 5, in the morning before the administration of the first dose of atenolol, and in the afternoon of Day 9, the brachial artery and vein of subjects were cannulated. The tip of the venous catheter was advanced into the right atrium. Brachial artery pressure was detected with a Statham P23Db pressure transducer. Mean arterial pressure was derived by electronic integration. Heart rate was recorded continuously by electrocardiography. Simultaneously with the cardiac output measurements by the CO₂ rebreathing method, cardiac output also was measured in duplicate by the dye-dilution method, using indocyanine green. On Day 5, measurements were repeated 4 hours after the first dose of atenolol. Stroke volume (ml) and total peripheral resistance (mm Hg/liter min⁻¹) were calculated.

Plasma volume was measured with ¹²⁵I radioiodinated human serum albumin, with single sampling at 10 minutes, on Day 5 before the first dose of atenolol and on Day 9.

Heart Rate Response to Submaximal Ergometric Exercise

To assess the degree of beta-adrenergic inhibition of the heart by atenolol, submaximal ergometric exercise was performed on all subjects on Day 5 before atenolol therapy and on Day 9 during atenolol therapy. For each subject, the ergometer was set at a constant load, which was shown prior to the study to produce a heart rate greater than 115 beats/min after 4 minutes of exercise. The maximum heart rate achieved was obtained from a 15-second strip of the electrocardiogram. Load and duration of exercise for a given subject were the same on Days 5 and 9.

Plasma Renin Activity

Blood for plasma renin activity (PRA) determination was drawn in the morning of Day 4 (placebo) and Day 8 (atenolol) after the subjects were standing or walking for 1 hour. The blood was processed and centrifuged at room temperature, and the plasma was stored at -20°C. The PRA was determined by radioimmunoassay of angiotensin I, and the PRA values were related to the urinary sodium excretion during the 24-hour period that preceded the drawing of blood.
Table 1. Supine Blood Pressures and Heart Rates of 12 Hypertensive Subjects During Days 1 to 4 of the Inpatient Placebo Period

<table>
<thead>
<tr>
<th>Time</th>
<th>SBP</th>
<th>DBP</th>
<th>HR</th>
<th>SBP</th>
<th>DBP</th>
<th>HR</th>
<th>SBP</th>
<th>DBP</th>
<th>HR</th>
<th>SBP</th>
<th>DBP</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 am</td>
<td>156 ± 22</td>
<td>100 ± 8</td>
<td>84 ± 12</td>
<td>161 ± 23</td>
<td>101 ± 8</td>
<td>87 ± 10</td>
<td>147 ± 24</td>
<td>98 ± 10</td>
<td>87 ± 10</td>
<td>146 ± 22</td>
<td>96 ± 13</td>
<td>84 ± 16</td>
</tr>
<tr>
<td>2 pm</td>
<td>158 ± 26</td>
<td>98 ± 11</td>
<td>85 ± 10</td>
<td>147 ± 16</td>
<td>92 ± 8</td>
<td>78 ± 7</td>
<td>143 ± 20</td>
<td>93 ± 11</td>
<td>83 ± 9</td>
<td>142 ± 20</td>
<td>96 ± 12</td>
<td>83 ± 10</td>
</tr>
<tr>
<td>5 pm</td>
<td>154 ± 21</td>
<td>99 ± 10</td>
<td>78 ± 14</td>
<td>152 ± 19</td>
<td>99 ± 10</td>
<td>74 ± 10</td>
<td>146 ± 18</td>
<td>96 ± 9</td>
<td>75 ± 10</td>
<td>146 ± 15</td>
<td>98 ± 10</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>8 pm</td>
<td>151 ± 15</td>
<td>96 ± 9</td>
<td>77 ± 10</td>
<td>152 ± 19</td>
<td>94 ± 12</td>
<td>74 ± 11</td>
<td>150 ± 15</td>
<td>96 ± 9</td>
<td>76 ± 11</td>
<td>148 ± 16</td>
<td>95 ± 11</td>
<td>74 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SD. SBP and DBP = systolic and diastolic blood pressure in mm Hg units; HR = heart rate in beats/min.

Statistical Methods

The reported values are means with standard errors of the mean. The variability of the twice daily cardiac output measurements by the CO\textsubscript{2} rebreathing method in the 12 subjects during Days 2, 3 and 4 of placebo treatment was expressed as the mean ± SD and the coefficient of variation. Since there was no evidence of diurnal variation of hemodynamic parameters, the twice daily noninvasive hemodynamic measurements were averaged, except for Day 5, when atenolol therapy was started. Daily values were compared by analysis of variance for repeated measures on the same elements (individuals). Student's t test for paired replicates was used to compare measurements obtained during the placebo period and during atenolol therapy. Linear correlations between measured parameters in the same subject were calculated by standard statistical techniques.

Results

Four weeks after discontinuation of all antihypertensive medications, the supine and standing blood pressures of the 12 hypertensive subjects were 155 ± 6.6/101 ± 1.9 mm Hg (range: 122-184/92-110) and 155 ± 7.9/109 ± 3.2 mm Hg (range: 116-208/95-130) respectively. After an additional 4 days of placebo administration in the hospital, five patients were given 50 mg and seven patients 100 mg of atenolol for 5 days.

The supine resting blood pressures and heart rates of the 12 subjects during the in-hospital placebo period are shown in table 1. Supine diastolic blood pressures and heart rates reached a steady level by Day 2 and supine systolic blood pressures by Day 3 of the placebo period. On Day 5 just before the first dose of atenolol was 16 ± 3.2 beats/min. The variability of the twice daily cardiac output measurements by the CO\textsubscript{2} rebreathing method in the 12 subjects during Days 2, 3 and 4 of placebo treatment was calculated by standard statistical techniques.

Table 2. Variability of Twice Daily Cardiac Output Measurements (liter/min) by the CO\textsubscript{2} Rebreathing Method in 12 Subjects During Days 2, 3 and 4 of the Inpatient Placebo Period

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean ± SD*</th>
<th>Coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.10 ± 0.98</td>
<td>16.1</td>
</tr>
<tr>
<td>2</td>
<td>5.48 ± 0.67</td>
<td>12.2</td>
</tr>
<tr>
<td>3</td>
<td>7.55 ± 0.41</td>
<td>5.4</td>
</tr>
<tr>
<td>4</td>
<td>5.10 ± 0.64</td>
<td>12.5</td>
</tr>
<tr>
<td>5</td>
<td>5.69 ± 0.67</td>
<td>11.8</td>
</tr>
<tr>
<td>6</td>
<td>5.51 ± 1.17</td>
<td>21.2</td>
</tr>
<tr>
<td>7</td>
<td>5.41 ± 0.96</td>
<td>17.7</td>
</tr>
<tr>
<td>8</td>
<td>5.29 ± 0.89</td>
<td>16.8</td>
</tr>
<tr>
<td>9</td>
<td>4.51 ± 0.79</td>
<td>17.5</td>
</tr>
<tr>
<td>10</td>
<td>6.57 ± 0.79</td>
<td>12.0</td>
</tr>
<tr>
<td>11</td>
<td>3.74 ± 0.78</td>
<td>20.8</td>
</tr>
<tr>
<td>12</td>
<td>5.29 ± 0.33</td>
<td>6.2</td>
</tr>
</tbody>
</table>

*Values are the mean ± SD of six separate measurements in the same subjects.
before the first dose of atenolol, was unchanged 4 hours later, 110 ± 3.7 mm Hg. By the morning of Day 6, mean arterial pressure fell to 95 ± 2.7 mm Hg and remained unchanged for the rest of the atenolol treatment period. Mean arterial blood pressure during atenolol therapy fell by 10 mm Hg or more in all subjects except one. This one patient was receiving 100 mg of atenolol daily.

The cardiac output (CO rebreathing) response to the initiation of atenolol therapy was biphasic (fig. 1, panel B). Cardiac output, 5.49 ± 0.30 liters/min, on Day 5 before the first dose of atenolol fell to 4.24 ± 0.21 liters/min 4 hours later (p < 0.01). During the next two days, cardiac output gradually returned to baseline, being 5.50 ± 0.29 liters/min on Day 7. A secondary fall in cardiac output occurred during Days 8 and 9. Cardiac output on Day 9, 4.68 ± 0.25 liters/min, was significantly reduced compared to values obtained on Day 7 (p < 0.02 liters/min). The individual cardiac output responses of the 12 subjects on Days 5, 7, and 9 are shown in figure 2. All subjects, except one (dashed line), showed to a greater or lesser extent the same cardiac output response. The one exception was the subject who failed to respond to the antihypertensive action of atenolol. The initial (4 hours) and late (Day 9) reductions in cardiac output were directly related to the control cardiac output in the morning of Day 5 (r = 0.72, n = 12, p < 0.01, and r = 0.69, n = 12, p < 0.05).

The calculated total peripheral resistances reflected the changes in mean arterial pressure and cardiac output (fig. 1, panel C). Total peripheral resistance rose initially, then fell by Days 6 and 7. If we excluded the one patient who did not respond to the antihypertensive effect of atenolol, the fall of total peripheral resistance below control values on Day 7 would have been statistically significant (p < 0.01, n = 11). Total peripheral resistance returned to baseline on Days 8 and 9.

**Figure 1.** Daily mean arterial pressures, cardiac outputs, and calculated total peripheral resistances in 12 hypertensive subjects during placebo and atenolol administration. Wide and narrow rectangles represent the average of twice daily and single measurements respectively. Vertical bars represent the standard error of mean. Statistical comparisons were made by analysis of variance for repeated measures on the same elements (individuals).

**Figure 2.** Daily cardiac output measurements in 12 hypertensive subjects during placebo administration (Day 5 am) and atenolol therapy (Day 5 pm to Day 9 pm). The dashed line represents the cardiac outputs of the one subject who failed to respond to the antihypertensive action of atenolol.
Results of the invasive hemodynamic measurements are shown in table 3. By 4 hours after initiation of atenolol therapy, heart rate was reduced 17 beats/min (mean). By comparison, the small additional reduction of heart rate, 4 beats/min (mean), by Day 9 was not statistically significant. Systolic, diastolic, and mean arterial pressures were unchanged initially, but fell by Day 9. The reduction in cardiac output 4 hours and 4 days after the start of atenolol therapy was the same. There were no significant changes in stroke volume in the course of atenolol therapy. Calculated total peripheral resistance values, based on the invasive measurements, were increased initially but returned toward baseline by Day 9.

Cardiac outputs measured simultaneously in the same subjects by the CO₂ rebreathing and the dye-dilution methods on Day 5 before the first dose of atenolol were highly correlated (r = 0.88, p < 0.01, n = 12) (fig. 3). Comparison of Day 5 pre-drug and Day 9 simultaneous measurements showed that the high correlation persisted (r = 0.81, p < 0.01, n = 24). There was also a good correlation between atenolol-induced acute changes in cardiac output, measured by the two methods, on Day 5 (r = 0.76, p < 0.01, n = 12).

Plasma volumes, 3110 ± 100 ml (n = 12), on Day 5 before atenolol were reduced to 2850 ± 100 by Day 9 (p < 0.01). The body weight of the 12 subjects on Day 5, 84.9 ± 3.90 kg, did not change significantly by Day 9, 84.2 ± 3.64 kg. Changes in plasma volume between Days 5 and 9 did not correlate with the corresponding changes in cardiac output, measured by dye-dilution (r = 0.22). Finally, 1-hour ambulatory PRA was 1.1 ± 0.29 ng/ml/hr (n = 10) on Day 4 during the placebo period and 0.8 ± 0.24 on Day 8 during atenolol therapy (p > 0.05). The 24-hour urinary sodium excretion measured on the day before the PRA measurement was 120 ± 18.0 mEq (n = 10) during the placebo period and 124 ± 13.6 mEq (n = 10) during the atenolol treatment period. Based on a nomogram relating 1-hour ambulatory PRA to 24-hour urinary sodium excretion, obtained in our laboratories, at least three of our subjects had low-renin hypertension, including the patient who failed to respond to the antihypertensive action of atenolol. Renin studies were not available in two subjects.

**Discussion**

The noninvasive technique of cardiac output measurements by the CO₂ rebreathing method offers an unique opportunity for frequent, sequential hemodynamic measurements in the same subjects. In this study, we have confirmed our previous findings of good reproducibility and accuracy of the CO₂ rebreathing method for measuring cardiac outputs. The technique allowed us to describe the hemodynamic sequence of events that accompanies the onset of antihypertensive action of a beta-adrenoceptor antagonist in more detail than has been done previously. A better description of these early

<table>
<thead>
<tr>
<th>Table 3. Invasive Systemic Hemodynamic Measurements in 12 Hypertensive Subjects During Placebo Administration (Day 5, am), 4 Hours After the First Dose of Atenolol (Day 5, pm), and After 4 Days of Atenolol Therapy (Day 9, pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
</tr>
<tr>
<td>Cardiac output (liter/min)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
</tr>
<tr>
<td>Total peripheral resistance (units)</td>
</tr>
</tbody>
</table>

Values are means ± SE.

* p < 0.001, for comparison of values during placebo and atenolol administration.
† p < 0.05, for comparison of values during placebo and atenolol administration.
‡ p < 0.02, for comparison of values during placebo and atenolol administration.
HEMODYNAMICS OF BETA-INHIBITION/Simo et al.

The initial systemic hemodynamic response to the administration of nonselective beta-adrenoceptor inhibitors is a fall in heart rate and cardiac output and a rise in total peripheral resistance, with the mean arterial pressure remaining unchanged. Acute administration of cardioselective beta inhibitors appears to have the same systemic hemodynamic effect, although in one study comprising a small number of young hypertensive patients, the antihypertensive effect of metoprolol was apparent within 15 minutes of administration. Our observations of the immediate systemic hemodynamic effects of a cardioselective beta inhibitor, atenolol, are in line with those of the majority of previous investigators. The direct correlation that exists between the control values of heart rate and cardiac output and the magnitude of their reductions after the initiation of beta-inhibitor therapy suggests that the initial hemodynamic response is in part determined by the prevailing cardiac beta-adrenergic tone.

The rise in calculated total peripheral resistance immediately following the administration of nonselective beta inhibitors appears to be mediated through cardiovascular reflex mechanisms and is associated with increased alpha-adrenergic vasoconstrictor tone. An increased circulating level of catecholamines may also play a role in the rise of total peripheral resistance. Increased alpha-adrenergic vasoconstrictor tone persists during long-term administration of nonselective beta inhibitors and may be accompanied by an exaggerated alpha responsiveness. The reflex cardiovascular adjustments that follow the acute administration of cardioselective beta-inhibitors have been less well studied. However, long-term treatment of hypertensive patients with atenolol is associated with elevated plasma norepinephrine levels, indicating increased sympathetic nervous system activity, both at rest and after exercise.

The initial fall in cardiac output following the initiation of beta-inhibitor therapy, in addition to triggering the reflex adjustments in alpha-adrenergic vasoconstrictor tone, appears to result in other peripheral vascular adjustments that oppose vasoconstriction. There is insufficient evidence at the present time to suggest whether these hemodynamic adjustments are mediated neurally or humorally. This may have been the reason why the reverse autoregulatory theory of the mechanism of action of beta inhibitors was proposed. According to this theory, the decrease in blood flow through all or some regional vascular beds gradually leads to a decrease in total peripheral resistance and a return of cardiac output to baseline values in an attempt to restore blood flow to meet tissue metabolic demands. There is experimental evidence that the time course of this type of autoregulatory response may be as brief as a few days.

The gradual return of cardiac output and of calculated total peripheral resistance toward baseline values in our subjects on the second and third day of atenolol therapy is compatible with some type of autoregulatory adjustment. It should be pointed out, however, that recently there has been considerable criticism of the autoregulatory theory of long-term blood pressure control. Significantly, some of this criticism has been raised in the context of long-term blood pressure control during beta-inhibitor administration. Antihypertensive therapy with beta inhibitors lowers cardiac output and increases oxygen extraction without appreciably changing oxygen consumption and metabolic rate. Beta-inhibitor therapy prevents the rise of cardiac output during the developmental stages of hypertension in spontaneously hypertensive rats and in DOCA-salt-treated dogs but does not prevent chronic hypertension, suggesting that vasoconstriction can occur in the absence of tissue hyperperfusion. The present study cannot resolve the controversy regarding the role of autoregulatory mechanisms in short- or long-term blood pressure control. It simply adds a new set of observations to the debate.

The hemodynamic mechanisms responsible for the secondary fall in cardiac output that we observed during atenolol therapy are equally speculative. There is little evidence to suggest that the fall of cardiac output during beta-inhibitor therapy is secondary to the reduction in plasma volume. In our patients, we were unable to establish a direct relationship between reductions in plasma volume and cardiac output. While reduction of cardiac output during long-term beta-inhibitor therapy is a frequent finding, previous measurements of plasma volume have yielded variable results, some investigators finding an immediate or long-term reduction in plasma volume, and some reporting unchanged or increased plasma volume.

A more consistent finding has been a redistribution of extracellular fluid volume between the intravascular and the extravascular space, indicated by a reduction of the plasma-to-interstitial-fluid-volume ratio. This new equilibrium between plasma and interstitial fluid volume has been described during the administration of both nonselective and cardioselective beta inhibitors. Increased capillary hydrostatic pressure secondary to a predominant and unopposed alpha-adrenergic venoconstrictor tone has been proposed as the mechanism responsible for the displacement of fluid from the intravascular to the extravascular space. Frequent, perhaps daily, measurements of the plasma-to-interstitial-fluid-volume ratio may be needed to explain the secondary fall in cardiac output that we have observed. Alternatively, the changes in cardiac output may be related to a redistribution of intravascular volume between the cardiopulmonary and peripheral vascular beds. In this regard, Tarazi and coworkers did not find a change in cardiopulmonary blood volume during long-term propranolol therapy, despite a 20% reduction in cardiac output.

The changes in PRA in our subjects during atenolol therapy were small and inconsistent. However, the ini-
tial PRAs of our subjects were low, reflecting their age, and there were at least three patients with low-renin hypertension, including the one who failed to respond to the antihypertensive action of atenolol. It is unlikely that changes in PRA played a major role in the hemodynamic sequence of events that we observed. More frequent measurements of PRA and the inclusion of study subjects with high- and normal-renin hypertension will be needed to determine the precise role of PRA in the hemodynamic sequence of events that follows the initiation of beta-inhibitor therapy.

Finally, our findings may be applicable not only to antihypertensive therapy with beta inhibitors but also to antihypertensive therapy in general. Sequential hemodynamic measurements using invasive laboratory procedures have been made previously to investigate the mechanism of action of diuretics and of alpha-adrenergic blocking agents. In pento-barbital-anesthetized dogs, the immediate hemodynamic effects of diuretics are similar to those of beta inhibitors, namely, a reduction in cardiac output without a change in mean arterial pressure. In hypertensive patients treated with diuretics, the reduction of cardiac output lasts for several weeks. In some patients, cardiac output may return toward baseline values after several months of antihypertensive therapy with diuretics. This delayed return of cardiac output toward control values has been referred to as "long-term autoregulation," the mechanisms of which appear to be different from the short-term autoregulation that we observed in the present study. The sequential hemodynamic effects of guanethidine are in many respects similar to those of diuretics, suggesting long-term rather than short-term autoregulatory adjustments. Frequent noninvasive systemic hemodynamic measurements will have to be made to ascertain whether the short-term systemic hemodynamic adjustments that we observed here are unique to the cardioslective beta inhibitors, or whether they also occur with the nonselective beta inhibitors and other antihypertensive agents.

Acknowledgments

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