Hemodynamics, Biochemical and Reflexive Changes Produced by Atenolol in Hypertension

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SUMMARY  Hemodynamic (systemic and regional), metabolic and cardiovascular reflexive variables were measured before and after 4 weeks of \( \beta \)-blockade with atenolol in 10 patients with mild essential hypertension. Atenolol reduced mean arterial pressure, heart rate, cardiac index (all \( p < 0.005 \)) and renal vascular resistance (\( p < 0.01 \)) and increased total peripheral resistance (\( p < 0.005 \)). Glomerular filtration rate and renal blood flow were unchanged; plasma renin activity fell 43%. Reflexive cardioacceleration during the Valsalva maneuver and upright passive tilt was blunted. No changes were observed in circulating fluid volumes.

In six patients followed for 1 year, blood pressure and heart rate were maintained at levels similar to those during the first 4 weeks. Atenolol was shown to be an effective oral antihypertensive that has no apparent deleterious hemodynamic effects on the renal and splanchnic circulations.

ALTHOUGH the efficacy of \( \beta \)-adrenergic blocking drugs for treating essential hypertension is established, the mode of action of these agents is not known. Changes in cardiac output, plasma renin activity, baroreceptor sensitivity and catecholamine release have all been postulated. Prolonged use of \( \beta \)-adrenergic inhibiting drugs has been demonstrated to reduce renal blood flow.\(^1\)\(^-\)\(^3\) This report details the prolonged hemodynamic and other physiologic effects of atenolol, a cardioselective \( \beta \)-blocking agent that lacks intrinsic sympathomimetic or membrane-stabilizing properties.

Methods

Patients and Protocol

Ten patients with mild essential hypertension, eight men and two women, eight white and two black, mean age 44 years (range 30 to 54 years), constituted the study group. All were extensively evaluated to exclude secondary hypertension. Exclusion criteria included greater than grade II hypertensive funduscopic changes, valvular heart disease, ativoventricular block, recent myocardial infarction, renal disease manifested by hematuria, proteinuria, or serum creatinine above 1.8 mg/100 ml; hepatic dysfunction evidenced by a total bilirubin above 1.1 mg/100 ml; insulin-dependent diabetes mellitus; history of adverse reaction to \( \beta \)-blocking drugs; chronic obstructive lung disease; and bronchial asthma.

Once patients were enrolled, all medications were discontinued for at least 2 weeks. At the end of that time, if diastolic pressure (phase V, Korotkoff) in the seated position was 90–120 mm Hg, placebo therapy was given for 3 weeks, after which systemic and regional hemodynamics were determined. Atenolol, 100 mg/day, was then started and maintained at that dose throughout the study. Patients were followed every 2 weeks until the end of a 4-week period, when the hemodynamic studies were repeated.\(^1\)\(^-\)\(^6\) Six patients were maintained on this dose, and outpatient blood pressure monitored for 1 year with monthly office visits.

Hemodynamic evaluation was performed by the standard methods of this laboratory.\(^6\) Continuous intraarterial and venous pressures were obtained on a 12-channel Electronics for Medicine indirect-writing recorder using a Statham P-23Db transducer. Supine cardiac output was determined in triplicate, using indocyanine green in the postabsorptive state. Central blood volume was calculated from the dye-dilution curve and represents the blood volume from the tip of the venous catheter in the superior vena cava to the tip of the arterial catheter in the ascending aorta just proximal to the subclavian artery.\(^7\) Hemodynamic indexes were calculated by standard formulas using a programmed Hewlett-Packard computer.\(^1\)\(^-\)\(^6\)

Renal blood flow was determined concomitantly by single-injection clearance of \( ^{131} \)iodinated-para-aminophipuric acid (\( ^{131} \)I-PAH).\(^6\) Splanchnic blood flow was estimated by injecting 50 mg of indocyanine green, using methods previously described.\(^6\) Renal and splanchnic vascular resistances were calculated by dividing the mean arterial pressure by the respective regional blood flow, then multiplying by 100 (i.e., \( [\text{MAP/RBF}] \times 100 \)).

Plasma volume was determined during the hemodynamic study by injecting \( ^{131} \)I-human serum albumin into the venous line and measuring the decline of plasma radioactivity after 15 and 30 minutes of equilibration.\(^6\) Red cell mass was measured simultaneously by injecting \( ^{51} \)Cr-labeled red blood cells into the venous line and measuring the concentration of the isotope in the arterial blood after 20 minutes equilibration.\(^6\) Total blood volume was the sum of the plasma volume and red cell mass.

Plasma renin activity was measured according to the method of Sealey et al.\(^8\) Plasma catecholamines (norepinephrine and epinephrine) were determined by radioenzymatic assay.\(^11\)

Valsalva maneuver was performed (after instruction) by forced expiration against a closed glottis for 30 seconds. When baseline values were reattained,
each patient was passively tilted upright at 50°, and after 5 minutes, hemodynamic measurements were obtained. After supine reequilibration to baseline status, isometric handgrip exercise was performed to one-third of previously ascertained maximum voluntary contraction using a standardized sustained handgrip apparatus. During the third minute of sustained handgrip, systemic hemodynamic variables were again measured.13

Glomerular filtration was determined by endogenous creatinine clearance using standard methods. Statistical analysis was performed using the paired t test.

**Results**

Atenolol reduced mean arterial pressure from 109 to 99 mm Hg, heart rate from 62 to 51 beats/min and cardiac index from 3.37 to 2.68 l/min/m² (all p < 0.005). Total peripheral resistance increased from 32.6 to 37.5 U (p < 0.05) (table 1). Stroke index and left ventricular ejection rate did not change.

Atenolol maintained renal and splanchnic blood flow and reduced renal vascular resistance from 24.9 to 20.9 U (p < 0.01). Intravascular volumes did not change with treatment, nor did intravascular distribution (cardiopulmonary/total blood volume ratio) (table 2).

Creatinine clearance was maintained. Plasma renin activity fell 43%, from 0.66 to 0.38 ng/ml/hour. In contrast, plasma norepinephrine rose, from 201 vs 317 pg/ml (p < 0.05), but plasma epinephrine did not change (table 3).

During the Valsalva maneuver, cardioacceleration and systolic blood pressure rise were blunted by atenolol (16% vs 5% and 46% vs 27%, respectively, both p < 0.05). Cardioacceleration was blunted during passive upright tilt (17% vs 6%, p < 0.05). No significant changes occurred during isometric handgrip exercise (table 4).

### TABLE 1.  **Systemic Hemodynamic Measurements Before (Control) and During Atenolol Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>109 ± 5</td>
<td>99 ± 6†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>62 ± 3</td>
<td>51 ± 2†</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.37 ± 0.15</td>
<td>2.68 ± 0.10†</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>58 ± 1</td>
<td>54 ± 1</td>
</tr>
<tr>
<td>Cardiopulmonary volume (ml)</td>
<td>2661 ± 140</td>
<td>2651 ± 172</td>
</tr>
<tr>
<td>Left ventricular ejection rate (ml/sec/m²)</td>
<td>165 ± 3</td>
<td>155 ± 2</td>
</tr>
<tr>
<td>Total peripheral resistance (U)</td>
<td>33 ± 2</td>
<td>38 ± 3*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*p<0.05.

†p<0.005.

### TABLE 2.  **Regional Hemodynamics and Volume Measurements Before and During Atenolol Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood flow (ml/min/m²)</td>
<td>461 ± 26</td>
<td>498 ± 28</td>
</tr>
</tbody>
</table>
| Renal vascular resistance (U) | 24.9 ± 2.6 | 20.9 ± 1.8*
| Splanchnic blood flow (ml/min/m²) | 407 ± 6 | 345 ± 6 |
| Splanchnic vascular resistance (U) | 29.8 ± 1.0 | 32.8 ± 1.0 |
| Plasma volume (ml) | 3088 ± 118 | 3098 ± 130 |
| Total blood volume (ml) | 5058 ± 191 | 5049 ± 200 |
| Cardiopulmonary/total blood volume | 0.53 ± 0.02 | 0.53 ± 0.03 |

Values are mean ± SEM.  
*p<0.01.

### TABLE 3.  **Metabolic and Biochemical Measurements Before and During Atenolol Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>107 ± 4</td>
<td>102 ± 5</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hour)</td>
<td>0.66 ± 0.27</td>
<td>0.38 ± 0.13</td>
</tr>
<tr>
<td>Plasma norepinephrine (pg/ml)</td>
<td>201 ± 3</td>
<td>317 ± 7*</td>
</tr>
<tr>
<td>Plasma epinephrine (pg/ml)</td>
<td>67 ± 3</td>
<td>88 ± 4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.  
*p<0.05.

Atenolol significantly reduced supine and standing systolic and diastolic pressures and heart rate (p < 0.005) (table 5). These effects persisted for 1 year in six patients who remained on treatment long-term (table 6). No clinical or biochemical adverse effects were observed, and the drug was well tolerated by all patients.

### Discussion

This study confirms the effectiveness of atenolol in a single daily dose for patients with mild to moderately severe essential hypertension. Outpatient blood pressure control was achieved in both supine and standing positions.

The hemodynamic results demonstrate a significant fall in mean arterial pressure and heart rate that was associated with a reduced cardiac index and an increased total peripheral resistance. In contrast to the effect of other β-blocking drugs,1 atenolol did not reduce renal blood flow, and renal vascular resistance fell as glomerular filtration was maintained. Plasma renin activity fell 43%.

As in other regional circulations, α- and β-adrenergic receptors are present in the renal vascular bed and in the juxtaglomerular apparatus in the kidney.13 14 Renal vasoconstriction has been observed...
TABLE 4. Reflexive Changes Before (Control) and During Oral Atenolol Therapy

<table>
<thead>
<tr>
<th>Valsalva maneuver</th>
<th>Control</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ↑ heart rate (DIP)</td>
<td>16 ± 1</td>
<td>5 ± 2*</td>
</tr>
<tr>
<td>% ↑ systolic pressure (overshoot)</td>
<td>46 ± 2</td>
<td>27 ± 2*</td>
</tr>
<tr>
<td>% ↑ diastolic pressure (overshoot)</td>
<td>40 ± 2</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Upright tilt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ↑ heart rate</td>
<td>17 ± 1</td>
<td>6 ± 1*</td>
</tr>
<tr>
<td>Δ mean arterial pressure (mm Hg)</td>
<td>8 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>% ↑ cardiac index</td>
<td>17 ± 1</td>
<td>13 ± 1</td>
</tr>
</tbody>
</table>

Isometric (handgrip) exercise

| % ↑ heart rate | 15 ± 2 | 13 ± 1 |
| % ↑ arterial pressure | 24 ± 1 | 28 ± 2 |
| % ↑ cardiac index | 14 ± 2 | 4 ± 1 |

Values are mean ± SEM. 
*p < 0.05. 
Abbreviations: ↑ = increase; ↓ = decrease; Δ = change; DIP = decrease in pressure.

TABLE 5. Outpatient Response to Atenolol Therapy in 10 Patients for 4 Weeks

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Therapy</td>
</tr>
<tr>
<td>Supine</td>
<td>146/96 ± 4/1</td>
</tr>
<tr>
<td>Standing</td>
<td>144/101 ± 4/1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. 
For both systolic and diastolic pressure, and heart rate: *p < 0.001. 
†p < 0.005.

dynamic actions were similar to those of propranolol and timolol, decreasing arterial pressure and reducing cardiac index, heart rate and plasma renin activity. In contrast to the effect of other β-blocking drugs, renal blood flow was maintained as renal vascular resistance fell. Plasma volume did not change during treatment with atenolol. Modifications of cardiovascular reflexes during atenolol therapy were relatively minor. The persistent hypertensive and bradycardic effects emphasize its value in the therapy of mild essential hypertension.20-28

References

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Hemodynamics, biochemical and reflexive changes produced by atenolol in hypertension.
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