Hemodynamic and Cardiac Effects of Centrally Acting Antihypertensive Drugs

EDWARD D. FROHLICH, FRANZ H. MESSERLI, BARBARA L. PEGRAM, AND MERRILL B. KARDON

SUMMARY The centrally acting α-adrenergic receptor agonist compounds have been available for treatment of hypertension for more than 25 years. Through studies of these compounds during this time, new knowledge has been made available not only on their mechanisms of antihypertensive action but also on the role of the adrenergic nervous system in essential hypertension. This discussion primarily reviews work from this laboratory on the cardiovascular actions of these compounds but reflects the general information from other quarters. In general, reduction of arterial pressure induced by these agents is associated with a cardiac output that remains relatively unchanged and with organ blood flows that are preserved. As a result of the reduced pressure, cardiac function is improved; and in recent studies, cardiac mass may be reduced. Associated with the reduced arterial pressure is an expanded plasma volume that is associated with a reduced blood viscosity, hematocrit, and plasma renin activity, but which may be at the expense of some return of arterial pressure toward pretreatment levels. The latter usually requires the addition of diuretic therapy. Current studies in our laboratory concern the performance of the heart following regression of ventricular hypertrophy both at reduced as well as increased ventricular afterloads.

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KEY WORDS • methyldopa • systemic hemodynamics • regional blood flows • left ventricular hypertrophy • regression of hypertrophy • ventricular function

THE centrally acting α-adrenergic receptor agonist compounds lower arterial pressure by inhibiting adrenergic outflow from brain stem centers to the cardiovascular system.1-2 The effect is control of abnormally elevated arterial pressure and often requires the addition of diuretics to minimize a secondary expansion of intravascular volume.3 4 The net result is lowered arterial pressure, preserved organ blood flow, improved cardiac function, and reduced cardiovascular morbidity and mortality.5 This report details a series of hemodynamic and cardiac studies in our laboratories1-2; however, the data presented are entirely consistent with the overall knowledge reported by others. For this reason, we shall restrict this discussion to data obtained clinically and experimentally by our investigative group. Specifically, we shall review cardiovascular changes brought about by central α-adrenergic receptor agonist treatment in patients with essential hypertension, supplementing these findings with data obtained experimentally from animals with another expression of naturally occurring hypertension, the spontaneously hypertensive rat (SHR). Studies in rats with Goldblatt (renovascular) hypertension also will be presented.

Methods

Clinical

All hemodynamic studies were performed in the morning with the patient fasting and without premedication. When these studies were performed to serve as controls for treatment, all antihypertensive therapy had been discontinued at least 4 weeks earlier (if therapy had been prescribed previously).5-7 Under these conditions cardiac output was measured with indocyanine green dye. Renal and splanchnic blood flows were determined from the disappearance of 131I-tagged paraaminohippurate and indocyanine green dye respectively, with methods reported earlier.8 Plasma volume and red cell mass were determined with 125I-iodinated human serum albumin and 51C-labeled red blood cells respectively. Responses to upright tilt (45 degrees), isometric exercise (handgrip), and Valsalva maneuver were determined as reported earlier.7-10 Plasma renin activity and catecholamines were determined according to the methods of Sealey et al.11 and Peuler and
Johnson\textsuperscript{12} respectively. Respiratory function was measured by standard spirometric methods. Measurements of blood viscosity were made at 37°C at the shear rate of 230 sec\textsuperscript{-1}, with a core-in-plate viscometer as described earlier.\textsuperscript{13}

**Experimental**

Studies with experimental hypertensive animals were performed using either the spontaneously hypertensive rat and its normotensive control, the Wistar-Kyoto (WKY) rat,\textsuperscript{14} or the two-kidney, one clip hypertensive (2K,1C) rat.\textsuperscript{15} In these hemodynamic studies, cardiac output and organ and regional blood flows were determined with 15 ± 5 μm diameter, radioisotopically tagged, carbonized microspheres and previously described methods that were validated in our laboratories for the rat.\textsuperscript{16-19} Other hemodynamic studies were designed to determine cardiac performance (i.e., pumping ability)\textsuperscript{20,21} of these experimental hypertensive rats treated (or not) with centrally acting α-adrenergic agonist compounds. The SHR were bred in our laboratory from the descendants of an original NIH progeny from Japan.\textsuperscript{14} The WKY American rats used for the 2K,1C studies had tantalum clips placed around one renal artery (methods described previously\textsuperscript{22}); their control rats were sham-operated.

**Hemodynamic Studies**

**Clinical**

Patients received methyldopa therapy by gradually increasing the daily dose from 250 mg twice daily to a maximum of 2 gm per day, depending on response of their arterial pressure. Both systolic and diastolic pressures were reduced significantly with therapy. Data reported earlier comparing younger and older patients showed similar control of arterial pressure in the two groups (Table 1).\textsuperscript{10} This pressure reduction was associated with a decrease in cardiac output in the older patients. The pressure fall in the younger patients was associated with a significant slowing of heart rate. These hemodynamic changes were associated with unchanged renal blood flow in both the younger and the older patients (1081 ± 115 to 1061 ± 77 and 904 ± 132 to 909 ± 172 ml/min respectively).\textsuperscript{10} Other hemodynamic studies with splanchnic blood flow and flow distribution to other vascular territories similarly showed no change.

**Experimental**

To supplement these clinical studies we determined the immediate (intravenous) and more long-term (gastric-tube feeding) hemodynamic effects of methyldopa in SHR and WKY rats.\textsuperscript{22} To determine the immediate effects, methyldopa was administered in a dosage of 40 mg/kg i.v.; to determine the prolonged (3 weeks) effects, methyldopa was administered every 12 hours by gavage tube (400 mg/kg/day). After intravenous administration, pressure fell in both WKY rats and SHR, but this fall was significant only for the WKY rats. This fall was associated with a significant fall in cardiac output in both the SHR and WKY rats; total peripheral resistance remained unchanged. In contrast, prolonged methyldopa treatment produced no change in pressure in the WKY rats but produced a significant pressure fall in SHR. In these more prolonged studies the reduction in pressure was associated with a decreased cardiac output in the SHR, but total peripheral resistance remained unchanged (Table 2).\textsuperscript{21}

In contrast to these hemodynamic findings with methyldopa, when clonidine (a similar central α-adrenergic agonist) was given (in doses of 25 μg/kg i.v. or 0.1 mg/kg/day by gastric-tube feeding) arterial pressure was not reduced in either SHR or WKY rats following the intravenous administration; but there was a pressure reduction similar to methyldopa with prolonged treatment. The pressure reduction in SHR produced by clonidine was associated with a decreased heart rate, whereas methyldopa administration increased heart rate.\textsuperscript{22}

With prolonged methyldopa and clonidine therapy, blood flow distribution to the major organs (skin, skeletal muscle, brain, heart, kidneys, and splanchnic organs) remained unchanged with both centrally acting alpha-adrenergic agonist compounds (Table 3).\textsuperscript{22}

**Table 1. Systemic Hemodynamic Changes Produced by Methyldopa in Younger and Older Patients with Essential Hypertension**

<table>
<thead>
<tr>
<th>Index</th>
<th>Younger patients</th>
<th>Older patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treated</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 (2.4)</td>
<td>—</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>172 (9)</td>
<td>153 (4)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>92 (3)</td>
<td>83 (2)</td>
</tr>
<tr>
<td>Mean</td>
<td>118 (4)</td>
<td>106 (2)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 (4)</td>
<td>65 (3)</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.2 (0.5)</td>
<td>6.1 (0.5)</td>
</tr>
<tr>
<td>Total peripheral resistance (U)</td>
<td>20.4 (2)</td>
<td>18.4 (2)</td>
</tr>
</tbody>
</table>

Each measurement represents the mean (± SEM).

*Adapted from Messerli et al.\textsuperscript{10}
Cardiac Mass and Function

In recent years a number of reports have indicated that certain antihypertensive drugs may decrease cardiac mass with prolonged treatment, but that this response is not necessarily associated with improved hemodynamic effects.\textsuperscript{22-33} Our studies in the SHR and WKY rats demonstrated that with prolonged methyldopa therapy there was a significant reduction in heart weight in both the normotensive WKY rats and the hypertensive SHR.\textsuperscript{22} Moreover, these changes in cardiac mass were unrelated to hemodynamic factors, including myocardial blood flow, particularly in the WKY rats (Table 3). In contrast to these findings, despite the same hemodynamic effects in the WKY rats and SHR, there was no change in cardiac mass following clonidine administration.\textsuperscript{22} When clonidine dose was tripled blood pressure did not decrease, but total peripheral resistance increased (presumably due to peripheral agonist effects of clonidine).\textsuperscript{23} Under these circumstances, however, cardiac mass was reduced.

It was of further interest that when the WKY rats and SHR were treated with hydralazine (5 mg/kg/day) there was a greater reduction in arterial pressure and total peripheral resistance than with the centrally acting adrenergic-suppressing compound and no change in cardiac output, yet cardiac mass remained unchanged.\textsuperscript{22} These studies suggest that additional factor(s) over and above the hemodynamic alterations must account for the reduced cardiac mass.\textsuperscript{22-33} This reduction in cardiac mass was associated with an increased hea

<table>
<thead>
<tr>
<th>Blood flows (ml/min/gm)</th>
<th>WKY rats</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>Immediate (i.v.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>0.10</td>
<td>0.12</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Brain</td>
<td>0.84</td>
<td>0.81</td>
</tr>
<tr>
<td>Heart</td>
<td>3.33</td>
<td>3.31</td>
</tr>
<tr>
<td>Kidneys</td>
<td>8.99</td>
<td>6.52\textsuperscript{†}</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>0.77</td>
<td>0.93</td>
</tr>
<tr>
<td>Prolonged (3 weeks)</td>
<td>(400 mg/kg/day)</td>
<td>(400 mg/kg/day)</td>
</tr>
<tr>
<td>Skin</td>
<td>0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Brain</td>
<td>0.84</td>
<td>0.86</td>
</tr>
<tr>
<td>Heart</td>
<td>3.33</td>
<td>4.70</td>
</tr>
<tr>
<td>Kidneys</td>
<td>9.39</td>
<td>7.64</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>0.77</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*From Pegram et al.\textsuperscript{22} \textsuperscript{†}p < 0.05, at least.
rate with methyldopa administration and a slower heart rate with clonidine administration; under both circumstances myocardial flow was maintained. Therefore, adrenergically mediated factors per se may not be the simple explanation for these divergent findings.

More recently, reversal of ventricular mass with prolonged methyldopa therapy was confirmed clinically by several groups of clinical investigators who used sequential M-mode echocardiographic measurements. Cardiac Performance

The question may be raised whether prolonged methyldopa treatment that produced regression in cardiac mass was associated with normal performance of the heart. This question is all the more important because experimental studies from other laboratories have demonstrated that the percentage of collagen tissue in the regressed heart may be greater than that observed without treatment. To determine cardiac performance of hypertrophy-regressed hearts, 2K,1C rats and their sham-operated controls were treated either with methyldopa or by unclipping the renal artery to reverse the hypertension. Cardiac performance was determined with an electromagnetic flowmeter under light ether anesthesia by assessing the response of cardiac output and left ventricular stroke work to a rapid infusion of saline over 1 minute, while also measuring left ventricular end-diastolic pressure.

In untreated 2K,1C rats cardiac performance progressively decreased after 4 and 6 weeks. After 4 weeks of 2K,1C hypertension in additional rats, one group remained clipped, a second group was unclipped, and a third group was treated with methyldopa (400 mg/kg/day). The groups were followed for 2 additional weeks on this treatment program and ventricular performance was assessed (6 weeks after initial clipping). As indicated previously, there was a further deterioration of left ventricular performance in the untreated 2K,1C rats as compared with those rats studied 4 weeks after clipping. The rats that were treated either by unclipping the renal artery or with methyldopa, however, demonstrated a regression of cardiac mass as compared with the still-hypertensive rats. This regression in mass was associated with an improved cardiac function (as assessed by pumping ability). It must be emphasized, however, that the cardiac performance was assessed in these rats with regressed cardiac mass when arterial pressure and total peripheral resistance were at normal or near-normal levels. Still remaining, therefore, is the critical question whether the performance of the heart would still be normal were pressure to have increased (following cessation of methyldopa therapy — or even, in the case of the renal artery clipped rats, following clip removal) to pretreatment levels. This question is currently being reevaluated, and preliminary studies indicate that when arterial pressure is abruptly increased by placing a snare around the ascending aorta, there is a deterioration in performance of the regressed-hypertrophied heart as compared with a normal heart.

Volume

It is well known that with prolonged antihypertensive therapy with adrenergic-inhibiting or vasodilating compounds a slow, but progressive, expansion of intravascular volume occurs as fluid returns from the extravascular to the intravascular compartment. To determine the more immediate changes in these fluid compartments, 14 patients with essential hypertension with high hematocrit values (average: 53.1 ± 0.4%) and contracted plasma volume (16.2 ± 0.4 ml/cm) were treated only with methyldopa for 4 weeks. The results of this study demonstrated that with treatment blood pressure was reduced significantly and that this fall in pressure was maintained despite progressive expansion of plasma volume (Table 4). Presumably, in the absence of this expanded plasma volume, arterial pressure might have fallen further. Nevertheless, associated with this plasma volume expansion was a reduction in venous hematocrit. That this fall in hematocrit was exclusively due to plasma volume changes was shown by unchanged red cell mass and serum erythropoietin level. Further, we also demonstrated that both blood and plasma viscosity were reduced over the 4-week treatment period, and associated with this decreased viscosity and expanded plasma volume was a

<table>
<thead>
<tr>
<th>TABLE 4. Effects of Methyldopa Therapy*</th>
</tr>
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<tbody>
<tr>
<td><strong>Control</strong></td>
</tr>
<tr>
<td><strong>1 week</strong></td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
</tr>
<tr>
<td>Plasma volume (ml/cm)</td>
</tr>
<tr>
<td>Red cell mass (ml/cm)</td>
</tr>
<tr>
<td>Venous hematocrit (vol %)</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
</tr>
<tr>
<td>Serum erythropoietin (IU/ml)</td>
</tr>
<tr>
<td>Blood viscosity (poise)</td>
</tr>
</tbody>
</table>

*Adapted from Chrysant et al.†

†p < 0.001 with reference to control levels.
progressive decrease in plasma renin activity. These studies therefore lend physiological credence to the observation that patients with high plasma renin activity may be predisposed to more cardiovascular complications. Under these circumstances the hemococoncentration could predispose the patient to microcirculatory rheological changes and associated vascular complications. Moreover, the results of our study showed that the state of high plasma renin activity and higher arterial pressure was associated with contracted intravascular volume and higher blood viscosity. Indeed, each of these factors could predispose the patient to vascular damage that might be prevented by reducing pressure, expanding plasma volume, and reducing blood viscosity.

Other Studies

Reflex Changes

To determine whether the methyldopa-treated patient maintains normal cardiovascular reflexive responses to frequently produced stimuli, patients were studied under controlled conditions that monitored responses to the Valsalva maneuver, isometric exercise, and upright tilt. These studies demonstrated that despite a significant reduction in circulating norepinephrine levels in both younger and older patients (346 ± 64 to 160 ± 26 and 566 ± 111 to 272 ± 57 pg/ml respectively; both p < 0.05, at least), qualitatively similar cardiovascular responses were maintained. Thus, despite a slight fall in arterial pressure with upright tilt, significant orthostatic hypotension did not occur. Similar qualitatively unchanged responses to isometric handgrip and Valsalva maneuver were also observed. These findings are similar to reports by others.

Pulmonary Function Studies

It was of interest to find no significant changes in either 1-second forced expiratory volume or vital capacity of either our younger or older patients treated with methyldopa. Both functions decreased by statistically insignificant amounts in our older patients.

Conclusions

Much clinical and experimental data have been amassed concerning the pathophysiology of essential and experimental hypertension with centrally active α-adrenergic-receptor agonists. These studies not only have provided considerable information concerning the role of the adrenergic nervous system and its inhibition in the pathophysiology and treatment of hypertension, but also have generated a number of pathophysiological questions that could be addressed only by long-term treatment and careful evaluation of the treated patients. These therapeutic studies not only have demonstrated the efficacy of long-term treatment with these compounds in patients with hypertension, they also have shown that prolonged reduction in pressure is associated with a maintained blood flow to the vital organs. That this reduction in pressure and maintained flow is due to reduced adrenergic outflow from the brain can be supported by reduced circulating levels of norepinephrine; however, whether this reduced adrenergic input to the heart and vessels is the factor that can be ascribed for the regressed ventricular mass associated with therapy remains to be determined. Nevertheless, the regressed mass does not seem to be totally dependent on the hemodynamic effects of the drug as cardiac mass also is reduced in normotensive animals that demonstrated no hemodynamic effects; and when two compounds having similar central and hemodynamic effects are used, disparate effects may be observed. Finally, it is appropriate to ask whether the reduced cardiac mass associated with methyldopa also benefits the functional reserve of the heart. Thus, even though improved ventricular afterload and hemodynamic functions are associated with the reduced mass, abrupt cessation of therapy could lead to a rapid return of pressure to pretreatment levels. Under these circumstances it is not clear whether the heart with regressed hypertrophy could perform normally at these high pressures and workloads. This question is currently under investigation.

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