Blood Pressure Regulation in Pheochromocytoma

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SUMMARY Two sets of studies were performed in 13 patients with proved adrenal pheochromocytoma to test the hypothesis that the sympathetic nervous system (SNS) is active and might contribute to the hypertensive state. Similar studies were performed in 15 additional patients considered to have essential hypertension. In the first set, 13 patients with pheochromocytoma were subjected to head-up tilt to assess the activity of the SNS. This maneuver decreased diastolic blood pressure in only two; heart rate increased appropriately in all except one. Changes in plasma norepinephrine (NE) were variable and did not correlate with changes in blood pressure (BP) and heart rate (HR).

In the second set, 10 patients with pheochromocytoma were given a single oral dose of clonidine (0.3 mg) to evaluate what role, if any, the SNS might contribute to the hypertensive state. Fifteen patients with essential hypertension were studied similarly for comparison. Clonidine produced significant decreases in BP and HR but left plasma renin activity unchanged in both groups. In essential hypertension, the cardiovascular responses were accompanied by significant reductions in plasma NE. By contrast, plasma NE was unchanged in patients with pheochromocytoma, despite similar reductions in BP and HR. These results suggest that the sympathetic reflexes are intact in pheochromocytoma, and that much of the hypertension associated with these tumors may be related to increased sympathetic activity. (Hypertension 4 (suppl II): II-193-II-199, 1982)

KEY WORDS • sympathetic nervous system • essential hypertension • adrenal pheochromocytoma • clonidine • catecholamines • smooth muscle • blood pressure regulation

THE hypertension that accompanies pheochromocytoma has generally been ascribed to the excessive circulating catecholamines released from the tumor. However, recent studies have demonstrated a marked discrepancy between the height of arterial pressure and the prevailing plasma catecholamine concentration; in fact, some of these patients may have long periods of normotension despite high circulating catecholamines. Lack of correlation between blood pressure (BP) and plasma catecholamine levels has been attributed to varying reactivity of vascular smooth muscle, and finally to receptor sensitivity.

One possibility that has received little attention is the active participation of the sympathetic nervous system (SNS) in BP control; although it has been assumed that sympathetic activity could be depressed in pheochromocytoma by the high catecholamine levels, this possibility has not been critically assessed in man. We therefore planned two sets of studies to assess that hypothesis. In the first, we used head-up tilt to determine the activity of the SNS. In the second, we administered clonidine (a centrally-acting antihypertensive agent that inhibits neurally-mediated catecholamine release) to evaluate, from changes in heart rate (HR), BP, plasma norepinephrine (NE) and plasma renin activity (PRA), the role of the SNS in the hypertension of pheochromocytoma.

In these studies, we found explicit evidence of intact sympathetic reflexes in patients with pheochromocytoma. In addition, we demonstrated that in these patients, clonidine rapidly decreased HR and BP to normal but had no effect on plasma catecholamines and PRA. Since clonidine decreases BP by inhibiting central sympathetic outflow and possibly presynaptic receptors as well, the results suggest that, despite the gross abnormality of catecholamines in pheochromocytoma, the hypertension associated with it must have an important neural component.

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Supported in part by Grant HL-6835 from the National Heart, Lung, and Blood Institute. Statistical analyses of graphs were performed with the PROPHET Computer System, which is supported in part by the Division of Research Resources of the National Institutes of Health.

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Methods

Patients

We studied 13 patients with surgically proven adrenal pheochromocytoma. In all patients, BP returned to normal after removal of the tumors, and concentrations of plasma catecholamines and urinary catecholamine metabolites were reduced to normal. Fifteen additional patients of similar age considered to have primary hypertension were studied similarly and served for comparison. At the time of study, all had been untreated for at least 2 weeks; details of the test were explained to each person and each freely consented to it.

Clinical Studies

The studies were performed in a quiet, warm, well-lighted clinical laboratory. The subjects were on 100-150 mEq Na diets and fasted for 10 hours overnight before the study. Blood was sampled from an intravenous cannula in a forearm vein kept patent with 0.9% sodium chloride solution containing 2 units of heparin per milliliter (2 U/ml). Brachial arterial BP was measured directly with a mercury sphygmomanometer. The HR was determined from an electrocardiographic tracing.

After 30 minutes of rest in the supine position and insertion of the intravenous cannula, control measurements of BP and HR were obtained three times at 5-minute intervals, and blood was drawn twice at 5-minute intervals for measurement of plasma catecholamines and PRA. Cardiovascular and humoral responses to either tilt or to clonidine administration were then assessed.

Tilt Studies

All 13 patients with pheochromocytoma underwent these studies. After control measurements, the patients were tilted head-up to 60° for 10 minutes. At this position, BP and HR were determined every minute. Blood was drawn for plasma catecholamines and PRA immediately before tilt and at the end of the 10-minute period. Following this, the patients were returned to the supine position.

Clonidine Studies

Ten patients (excepting Patients 5, 12, and 13) with pheochromocytoma and 15 patients with primary hypertension underwent these studies. After the control measurements, the patients received oral clonidine (300 µg as the hydrochloride) with 250 ml of water. Thereafter BP and HR were recorded at 30-minute intervals, and blood was sampled for plasma catecholamines and PRA at hourly intervals for 3 hours.

Biochemical Methods

Blood samples were drawn into 10 ml plastic syringes. Samples for plasma catecholamines were immediately transferred to precooled, heparin-treated tubes; those for PRA were transferred into ethylenediaminetetraacetic acid (EDTA)-treated tubes. Blood samples were kept on ice until plasma was separated in a refrigerated centrifuge at 4°C. Plasma was stored at −20°C before processing, and all specimens were assayed within 1 week of sampling. Samples from each patient were processed in a single run to avoid day-to-day variations in the assay.

The PRA was measured by a radioimmunoassay technique as previously described. Supine resting values on a regular sodium diet average 1.2 ± 0.4 (SD) ng/ml/hr in our laboratory. Plasma NE and epinephrine were determined in triplicate by a radioenzymatic assay described by Peuler and Johnson. The assay is sensitive to 5.0 pg/100 µl plasma for either catecholamine. The interassay coefficient of variation is 6% for NE and 10% for epinephrine. The mean values average 218 ± 92 (SD) ng/liter for NE and 42 ± 18 (SD) ng/liter for epinephrine.

Statistical Analysis

Statistical significance was tested by analysis of variance and Student's t test for unpaired data.

Results

Clinical Observations

Tilting head-up to 60° for 10 minutes was well tolerated by all patients with pheochromocytoma. Although some complained of cardiac awareness and exhibited excessive sweating and pallor, they were able to complete the study without adverse effects.

Clonidine was well tolerated by all patients. The only side effects were drowsiness and dryness of the mouth. Most patients slept through the period of study, none reported any symptoms on waking, and all were able to resume normal activity after the study. No symptomatic orthostatic hypotension was noted. None of the patients showed signs or symptoms suggesting a rebound phenomenon.

Pheochromocytoma: Cardiovascular and Plasma Catecholamine Responses to Tilt

Of 13 patients subjected to head-up tilt, only five demonstrated significant reductions in BP and of these, only two had a reduction in diastolic BP (table 1). However, in no patients was the BP decreased to hypotensive levels. All except one (Patient 9) showed an increased HR > 10 beats/min, a considerably higher value than that obtained in essential hypertensives.

Of eight patients whose BP increased with tilt, two (Patients 3 and 6) exhibited a fall in circulating catecholamines. In the five patients whose BP fell with tilt, plasma catecholamines increased in three, fell in one, and was unchanged in one. There was no correlation between the cardiovascular responses and the changes in plasma catecholamine concentrations.

In response to a similar maneuver, essential hypertensives exhibited the following changes: systolic BP
BLOOD PRESSURE REGULATION IN PHEOCHROMOCYTOMA/Bravo et al.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control</th>
<th>Tilt (60° head-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP (mm Hg)</td>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>Increased blood pressure:</td>
<td>1</td>
<td>188/122</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>140/94</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>150/106</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>164/92</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>162/115</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>194/114</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>164/74</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>142/84</td>
</tr>
</tbody>
</table>

Decreased blood pressure:

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control</th>
<th>Tilt (60° head-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP (mm Hg)</td>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>9</td>
<td>212/120</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>190/104</td>
<td>96</td>
</tr>
<tr>
<td>11</td>
<td>178/128</td>
<td>106</td>
</tr>
<tr>
<td>12</td>
<td>178/90</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
<td>162/104</td>
<td>94</td>
</tr>
</tbody>
</table>

BP = blood pressure; HR = heart rate; NE = plasma norepinephrine; E = plasma epinephrine.

was unchanged, diastolic BP increased by 13 ± 4 mm Hg, HR increased by 6 ± 3 beats/min, and plasma NE increased by 43%.

Primary (Essential) Hypertension: Cardiovascular and Humoral Responses to Clonidine Administration

Figure 1 illustrates the responses of a single patient, and table 2 details the results in 15 patients studied. In all patients, HR, BP and plasma NE fell significantly, but plasma epinephrine and PRA remained essentially unchanged. Changes in HR were correlated with baseline plasma NE (r = 0.64, p < 0.01) and with baseline plasma epinephrine (r = 0.53, p < 0.04). No significant correlations were found between basal catecholamines and basal BP; however, there was a significant correlation between absolute decrements of mean arterial pressure (MAP) and decrements of plasma NE (r = 0.43, p < 0.01).

Pheochromocytoma: Cardiovascular and Humoral Responses to Clonidine Administration

Figure 2 illustrates the responses of a single patient with pheochromocytoma, and table 3 summarizes the results in 10 patients studied. Although HR and BP fell significantly in every patient, neither plasma NE, plasma epinephrine, nor PRA were altered during the course of studies. There was no correlation, therefore, between plasma catecholamines and hemodynamic changes, in contrast with essential hypertensives and normotensives.
Table 2. Essential Hypertension: Cardiovascular and Humoral Responses to Clonidine

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Basal</th>
<th>Minutes after oral clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure (mm Hg):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>168±7</td>
<td>149*</td>
</tr>
<tr>
<td>diastolic</td>
<td>106±3</td>
<td>99*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>84±5</td>
<td>76*</td>
</tr>
<tr>
<td>Plasma catecholamines (ng/liter):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>norepinephrine</td>
<td>428±54</td>
<td>301*</td>
</tr>
<tr>
<td>epinephrine</td>
<td>59±10</td>
<td>50±7</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>2.71±0.53</td>
<td>2.61±0.58</td>
</tr>
</tbody>
</table>

All values are expressed as means ± SEM.

*Indicates a significance level of at least \( p < 0.05 \) compared to basal values.

Comparison Between Pheochromocytoma and Primary Hypertension

Before treatment, BP and HR were similar in both groups. In pheochromocytoma, they averaged 173/105 ± 23/10 (SD) mm Hg, and 90 ± 6 (SD) beats/min; in primary hypertension they averaged 168/106 ± 22/12 (SD) and 84 ± 20 (SD) (fig. 3). On the other hand, PRA differed significantly between groups: 5.36 ± 3.33 (SD) ng/ml/hr in pheochromocytoma, and 2.71 ± 2.04 (SD) in primary hypertension (\( p < 0.05 \)). Plasma NE was significantly higher in pheochromocytoma, 4321 ± 4062 (SD) ng/liter, than in primary hypertension, 428 ± 206 (SD) (\( p = 0.0002 \)).

Three hours after oral administration of 0.3 mg of clonidine, both groups exhibited similar and significant decreases in BP and HR; in both, PRA was unaltered. In primary hypertension, cardiovascular responses were associated with significant decreases in plasma NE. On the other hand, plasma NE was unchanged in pheochromocytoma patients, despite similar reductions in BP and HR.

Discussion

Results suggest that sympathetic activity is intact in pheochromocytoma and that, moreover, it may play an important role in the hypertension associated with this disorder. These conclusions were based on the demonstration of normal responses to head-up tilt and on the ability of clonidine to lower BP effectively. However, this interpretation relies on the extensively studied sympatholytic effect of clonidine; its antihypertensive action has been related by most investigators to a centrally-mediated decrease in

Figure 2. Cardiovascular and plasma norepinephrine (NE) responses to a single oral dose of clonidine (0.3 mg) in a patient with proved adrenal pheochromocytoma. For plasma NE, the solid line represents +2 SD above the mean values obtained from 60 healthy adult subjects of similar age.
TABLE 3. *Pheochromocytoma*: Cardiovascular and Humoral Responses to Clonidine

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Basal</th>
<th>Minutes after oral clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal 1</td>
<td>60</td>
</tr>
<tr>
<td>Blood pressure (mm Hg):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>173 ± 8</td>
<td>150*</td>
</tr>
<tr>
<td>diastolic</td>
<td>106 ± 3</td>
<td>99</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>91 ± 3</td>
<td>84*</td>
</tr>
<tr>
<td>Plasma catecholamines (ng/liter):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>norepinephrine</td>
<td>4321 ± 1254</td>
<td>6041</td>
</tr>
<tr>
<td>epinephrine</td>
<td>288 ± 92</td>
<td>363</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>± 1.11</td>
<td>± 1.10</td>
</tr>
</tbody>
</table>

All values are expressed as means ± SEM.
*Indicates a significance level of at least p < 0.05 compared to basal values.

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Peripheral sympathetic neural tone. Some have suggested that it may act on presynaptic $\alpha_2$-receptors to inhibit NE release. Our conclusions would still be valid whichever of the two views is accepted. Both actions produce the same final response — diminished outflow from the SNS with decreased circulating NE, which translates clinically into decreased arterial BP and HR and hemodynamically into decreased systemic vascular resistance and stroke volume.

Additional evidence in support of the concept that the cardiovascular effect of clonidine is predominantly due to inhibition of sympathetic activity and not to peripheral vascular effect may be summarized as follows: 1) oxymetazoline, an imidazoline derivative closely related to clonidine but which does not cross the blood-brain barrier, has been shown to exert similar effects at peripheral $\alpha_1$-adrenoceptors but to produce a pressor rather than a depressor response; 2) clonidine inhibits NE responses to insulin-induced hypoglycemia but increases sensitivity of vascular smooth muscle to intravenously administered NE; and 3) clonidine does not exert any depressor effect in subjects with chronic autonomic insufficiency or in those with chronic cervical spinal cord transection.

There is, therefore, convincing evidence that clonidine inhibits neurally-mediated catecholamine release and that it exerts this effect by stimulating central alpha-adrenergic receptors. On this basis, this reduction in BP by clonidine must mean that biologically effective release of NE from axon terminals is maintained in pheochromocytoma and could contribute to the hypertension. In addition, the demonstration that BP in pheochromocytoma was lowered despite persistently high levels of circulating catecholamines suggests that the NE released from...
axon terminals of sympathetic postganglionic neurons is biologically more significant than circulating catecholamines. This difference could be related to the easier access of NE released from preganglionic catecholamines. This difference could be related to the keeping with observations that these tumors do not possess sympathetic innervation. Clinical evidence that catecholamine release from pheochromocytoma does not result from activation of the SNS was presented by Hermann and Mornex. They detected no increase in urinary excretion of catecholamines in patients in whom hypoglycemia was induced by injection of insulin.

Sudden increases in BP may occur in pheochromocytoma as a result of mechanical compression of a tumor with massive catecholamine release. In some patients, however, spontaneous rises in BP may occur without detectable increases in plasma catecholamines. In these cases, it is reasonable to assume that this type of paroxysmal hypertension could be related to paroxysmal autonomic stimulation not unlike that seen in essential hypertension. Such a mechanism might also account for the hypertensive crises in some patients with pheochromocytoma that are evoked by emotional upset, pain, hyperventilation, or anesthesia.

Evidence has been presented that, in these patients, excessive stores of NE may accumulate in sympathetic nerve terminals such as occurs in patients receiving NE infusions. Engelmann and Sjoerdsma showed that tyramine injection into patients with pheochromocytoma caused increased excretion of urinary catecholamines and their metabolites, an effect that persisted for several days after tumor removal. In keeping with these findings, we found that high plasma NE values linger for about 1 week after complete tumor resection. That this is not due to surgical stress was demonstrated in patients undergoing surgery for aldosteronomas, who do not exhibit a similar pattern. Hengstmann and Dengler have also reported that following removal of a pheochromocytoma in three patients the daily excretion of catecholamines and their metabolites was still considerably elevated for about 1 week. It is not entirely clear how excessive stores of NE accumulate in sympathetic nerve terminals, but it could reflect increased neuronal uptake (such as occurs in platelets, red blood cells, and white blood cells) with increased circulating catecholamines. Whatever the reasons, given an intact SNS and increased stores of NE at sympathetic nerve terminals, any drug or maneuver increasing sympathetic activity, either directly or reflexly, could enhance catecholamine release and produce a hypertensive crisis. From this it follows that paroxysmal hypertension in pheochromocytoma need not be associated with increased catecholamine release from the tumor.

The present results also indicate that the renin-angiotensin system contributes little, if any, to the hypertension of pheochromocytoma since BP fell despite unchanged PRA. The failure to observe significant suppression of PRA contrasts with the results of others. In recent years, several investigators have reported that clonidine in addition to reducing BP and plasma NE also suppresses renin secretion. This has been observed in humans and the dog and it has been suggested that it results from a centrally-mediated decrease in sympathetic activity. However, the SNS is only one factor involved in the control of renin release, and several reports indicate that the SNS is not essential for renin release. In these studies, the major effect on renin release could have been mediated through a renal baroreceptor mechanism that was stimulated by the fall in BP. Reid and coworkers have shown experimentally in dogs that suppression of PRA by clonidine can be overcome by large falls in perfusion pressure. Finally, it should be emphasized that Wing et al. reported an increase in PRA in normotensive subjects who exhibited a decrease in BP after clonidine.

Our findings indicate that: 1) the renin-angiotensin system contributes little, if any, to the hypertension of pheochromocytoma; 2) the SNS is intact; and 3) much of the hypertension associated with pheochromocytoma may be related to increased activity of the SNS. In addition, our findings reaffirm the diagnostic value of plasma catecholamines in pheochromocytoma and raise the possibility of utilizing a centrally-acting antihypertensive agent, like clonidine, to control paroxysms of hypertension. The evidence that a centrally-acting agent can lower the BP despite high circulating catecholamines indicates that the hypertension of pheochromocytoma is not a simple, direct pressor response to increased circulating catecholamines.

There is no doubt that patients are usually cured by removal of the tumor. This suggests, first, that our observations cannot be fully explained by a coincidence of essential hypertension and a pheochromocytoma. More important, our findings raise the possibility that the increased sympathetic activity is in some manner intimately linked to the presence of an active pheochromocytoma. It would be sheer speculation to list hypothetical mechanisms, but the fact remains that the hypertension of pheochromocytoma was dependent in our patients both on the tumor and on the active adrenergic nervous system.

References


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Hypertension. 1982;4:193-199
doi: 10.1161/01.HYP.4.3_Pt_2.193

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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