A Reevaluation of the Hemodynamics of Pheochromocytoma

Emmanuel Bravo, Fetnat Fouad-Tarazi, Gianpaolo Rossi, Mitsukide Imamura, Wu-Wei Lin, M. Aziz Madkour, Pierre Wicker, Michael D. Cressman, and Manoel Saragoca

We examined the hemodynamic features of 24 untreated patients with surgically proven pheochromocytoma during steady-state periods and compared them with 24 untreated essential hypertensive patients individually matched for sex, age, body surface area, and arterial blood pressure. We found that, despite having 10-fold higher levels of circulating catecholamines, pheochromocytoma patients have hemodynamic characteristics similar to patients with essential hypertension and that, in individual patients, the ratio of circulating norepinephrine to epinephrine had no relation to the hemodynamic profile. In both groups, increased total peripheral resistance is primarily responsible for maintenance of hypertension. These results suggest that, unlike the acute administration of catecholamines, long-term exposure to high levels of circulating catecholamines does not produce hemodynamic responses characteristic of this group of compounds. This might be due in part to desensitization of the cardiovascular system to catecholamines and might explain the clinical observation that some patients can be completely asymptomatic despite harboring an actively catecholamine-secreting pheochromocytoma.

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Of all the secondary forms of hypertension, the mechanism of elevated arterial pressure in patients with pheochromocytoma seems to be the most straightforward. Because systemic administration of norepinephrine plus epinephrine increases cardiac rate and systemic vascular resistance, enhances myocardial contractility, and decreases venous compliance, the concept has evolved that pheochromocytoma is associated with a hyperkinetic, vasoconstrictive, hypovolemic form of hypertension. Although it is clear that the hypertensive crises of pheochromocytoma mimic the hemodynamic responses to acute administration of catecholamines, it is less clear if sustained exposure to high levels of circulating catecholamines produce a hemodynamic profile characteristic of the systemically administered hormones.

To address this question, we examined the hemodynamic features of patients with proven pheochromocytoma during steady-state periods and compared these findings with a group of essential hypertensive patients matched for sex, age, body surface area (BSA), and arterial blood pressure. The results suggest that during steady-state conditions, pheochromocytoma has hemodynamic features similar to essential hypertension despite having 10-fold higher levels of circulating catecholamines.

Methods

Patient Population

The study was performed in 24 patients with surgically proven pheochromocytoma and 24 essential hypertensive patients. All pheochromocytoma patients had documented hypertension. Three of these patients, however, were normotensive during the hemodynamic test. Essential hypertensive patients were either previously untreated or were taken off medications for at least 2 weeks. All but two pheochromocytoma patients were untreated at the time of study. One patient was on labetalol for up to 48 hours before the study, and a second patient required intermittent sublingual nifedipine (Procardia, Pfizer Inc., New York) to maintain diastolic blood pressures below 120 mm Hg. Both groups were on unrestricted diets. The two groups were individually matched for age, sex, weight, BSA, and arterial blood pressure (Table 1).

Methods

All studies were performed between 8:00 and 10:00 AM, after an overnight fast. Thirty minutes after insertion of a 21-gauge scalp vein needle and
supine rest, blood for plasma catecholamines (norepinephrine and epinephrine) was drawn, and radioiodinated albumin was injected intravenously for the measurement of plasma volume. After a 10-minute equilibration period, a second sample was obtained for radioactivity counting. Total blood volume was calculated from the simultaneous determination of packed cell volume using the following formula:

\[ BV = PV / (1 - Hct) \]

where BV is blood volume, PV is plasma volume, and Hct is hematocrit. The reproducibility of these measurements has been published elsewhere. Normal values for total blood volume are 30.9±3.0 (SD) ml/cm height for men, and 24.1±2.4 for women; normal values for plasma volume are 18.7±2.2 ml/cm height and 15.4±1.7 for men and women, respectively.

Cardiac output was measured by either thermodilution or "Tc radionuclide first-pass angiography; both methods yield comparable cardiac output values. Cardiac index, stroke volume, total peripheral resistance, and cardiopulmonary volume were calculated by conventional methods. Ejection fraction was obtained from equilibrium radionuclide (\(^{99m}\)Tc) ventriculography.

Plasma catecholamines were measured by the radioenzymatic technique of Peuler and Johnson. Normal values are 218±92 (SD) pg/ml for norepinephrine and 42±18 (SD) for epinephrine.

Statistical calculations were done with SAS Statistical Program (SAS Institute Inc., Cary, North Carolina) and based on the methods described by Snedecor and Cochran. Values are presented as mean±SEM. The Shapiro-Wilk test was used to determine the normality of data distribution. Unpaired \( t \) tests or nonparametric \( t \) tests were used to determine significance of differences between groups. Correlation coefficients were calculated by Pearson’s or Spearman’s method where appropriate. Differences were considered significant if the \( p \) value was less than 0.05.

**Results**

The demographic and clinical characteristics of the study population are shown in Table 1. The two groups were similar in sex distribution, age, BSA, and in the levels of systolic and diastolic blood pressure. Patients with pheochromocytoma had significantly higher plasma concentrations of norepinephrine and epinephrine than patients with essential hypertension. Also, the ratio of circulating plasma norepinephrine/epinephrine was significantly higher in pheochromocytoma patients than in essential hypertensive patients.

The hemodynamic profile of both patient groups is shown in Table 2. The hemodynamic features of pheochromocytoma were similar to those observed in patients with established essential hypertension. They differed only in the ratio of cardiopulmonary volume and total blood volume. The relations between diastolic blood pressure and plasma vol-

### Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pheochromocytoma</th>
<th>Essential hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F ratio</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>41.1±2.2</td>
<td>42.6±2.4</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.86±0.04</td>
<td>1.90±0.05</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>161±5</td>
<td>154±5</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>100±3</td>
<td>99±3</td>
</tr>
<tr>
<td>Plasma NE (pg/ml)</td>
<td>2,768±670*</td>
<td>223±67'</td>
</tr>
<tr>
<td>Plasma E (pg/ml)</td>
<td>223±67*</td>
<td>42±5</td>
</tr>
</tbody>
</table>

Values are mean±SEM. BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; NE, norepinephrine; E, epinephrine.

### Table 2. Hemodynamic Profile

<table>
<thead>
<tr>
<th>Hemodynamic indexes</th>
<th>Pheochromocytoma</th>
<th>Essential hypertension</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>121±3</td>
<td>119±3</td>
<td>87±10</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80±3</td>
<td>74±3</td>
<td>65±7.0</td>
</tr>
<tr>
<td>CI (ml/min/m²)</td>
<td>3,090±136</td>
<td>2,947±140</td>
<td>2,940±500</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>73±4</td>
<td>77±4</td>
<td>86±7.0</td>
</tr>
<tr>
<td>TPR (units-m²)</td>
<td>41±3</td>
<td>43±3</td>
<td>31±6.0</td>
</tr>
<tr>
<td>MTT (sec)</td>
<td>9±0.8</td>
<td>7±0.3</td>
<td>9.2±1.7</td>
</tr>
<tr>
<td>CPV (ml)</td>
<td>815±78</td>
<td>678±34</td>
<td>766±145</td>
</tr>
<tr>
<td>TBV (ml/cm Ht)</td>
<td>27.9±1.2</td>
<td>29.7±1.5</td>
<td>27.6±5.0</td>
</tr>
<tr>
<td>PV (ml/cm Ht)</td>
<td>16.7±0.7</td>
<td>18.0±0.9</td>
<td>17.2±2.6</td>
</tr>
<tr>
<td>CPV/TBV (%)</td>
<td>17.6±1.4*</td>
<td>13.7±0.6</td>
<td>17.5±1.3</td>
</tr>
<tr>
<td>EF (%)</td>
<td>67±3</td>
<td>62±2</td>
<td>54±3.0</td>
</tr>
</tbody>
</table>

Values for pheochromocytoma and essential hypertension are mean±SEM. Normal values are expressed as mean±SD (n=8). MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SV, stroke volume; TPR, total peripheral resistance; MTT, mean transit time; CPV, cardiopulmonary volume; TBV, total blood volume; Ht, height; PV, plasma volume; EF, ejection fraction.

*\( p < 0.005 \).
The hemodynamic features of hypertension asso-
ciated with pheochromocytoma have been inferred from the effects of intravenously administered nor
epinephrine and epinephrine. Thus, norepineph-
phrine producing tumors might be expected to increase arterial blood pressure by increasing total peripheral resistance while decreasing heart rate and cardiac output by reflex mechanisms. On the other hand, epinephrine producing tumors are expected to increase arterial blood pressure by raising cardiac output, heart rate, stroke volume, and left ventricular ejection rate. Pheochromocytoma patients, however, had hemodynamic characteristics similar to those observed in individually matched essential hypertensive patients despite having 10-fold higher plasma concentrations of catecholamines and significantly higher circulating plasma norepinephrine/epinephrine ratio.

In this study, pheochromocytoma patients had significantly elevated cardiopulmonary volume/total blood volume ratios when compared with the essential hypertensive group. The cardiopulmonary volume/total blood volume ratio is an estimate of the distribution of blood between the peripheral and central circulation. A significant increase indicates a redistribution of blood into the central circulation because of diminished capacity of reservoir vessels (venoconstriction) below heart level, whereas a significant decrease indicates increased capacity, presumably due to venodilation. Central redistribution of blood might be expected to occur in the presence of excessive levels of circulating catecholamines because of their potent venoconstrictive action. This effect of catecholamines, in turn, should result in increased cardiac output. Despite evidence of central redistribution of blood in pheochromocytoma, however, cardiac output was not increased. There are several possible explanations for this dichotomy. First, although there was a statistical difference in the cardiopulmonary volume/total blood volume ratio between pheochromocytoma and essential hypertension, the actual values were still within the normal range. Second, the development of structural changes in the heart (hypertrophy) could limit compliance of the ventricle. Third, myocardial damage due to exposure to high levels of circulating catecholamines might decrease myocardial contractility. Fourth, marked loss of \( \beta_1 \)-adrenergic receptors in the heart could diminish the cardiac response to circulating catecholamines. In patients with pheochromocytoma, in the absence of cardiac symptoms or other clinical evidence of cardiac involvement, echocardiographic findings are usually normal.

Clinical observations that the vasculature of patients with pheochromocytoma exhibit refracto-
riness to catecholamines could explain failure to demonstrate differences in hemodynamic character-
istics between essential hypertension and pheochromocytoma despite 10-fold higher plasma cate-
cholamine levels in patients with the latter. It is noteworthy that, in the present study, a significant relation was found between diastolic blood pressure and plasma norepinephrine/epinephrine ratio.

This correlation, however, was barely statistically significant \( (p<0.05) \), and elimination of one patient would have reduced this relation to an insignificant level.

Prolonged stimulation of tissues by adrenergic agonists can lead to diminished responsiveness of the tissues to subsequent activation by catecholamines; this phenomenon has been termed desen-
sitization or tachyphylaxis. Tsujimoto and coworkers examined the in vivo consequences of prolonged stimulation of vascular \( \alpha \)-adrenergic

![Graph](image.png)

**Figure 1.** Scatterplot showing relation between blood pressure and total peripheral resistance in pheochromocytoma. Solid and broken lines indicate mean and 95% confidence limits, respectively. Highly significant positive correlation suggests that hypertension is maintained by increased total peripheral resistance.
receptors in rats harboring norepinephrine-producing tumors. They found that in the early stages of the disease, loss of sensitivity was observed for both α₁- and α₂-adrenergic agonists, whereas responsiveness to Arg-vasopressin and angiotensin II was intact (homologous desensitization). In the later stages of pheochromocytoma, however, pressor responses to all three vasoconstrictive agents were subsensitive (heterologous desensitization). Additionally, radioligand binding studies showed that the α₁-adrenergic receptor number decreased 36% in mesenteric artery plasma membrane for these rats, whereas α₂-adrenergic receptor number was unaltered. These results are consistent with the work of Snively et al, showing adrenergic receptor down-regulation in experimental pheochromocytoma, and they also provide support for the observation that patients can be normotensive or only moderately hypertensive despite having levels of catecholamines that would usually produce marked increases in blood pressure when given acutely.

Long-term exposure to high levels of circulating catecholamines does not produce hemodynamic responses characteristic of the cardiovascular system to catecholamines or to structural and functional changes that tend to mask the effect of catecholamines. Clinically, this might explain why patients with pheochromocytoma can be completely asymptomatic for periods of time despite having high circulating levels of catecholamines.

References

KEY WORDS • hemodynamics • pheochromocytoma • essential hypertension • catecholamines
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