Sympathetic System Function and Vascular Reactivity in Hypercalcemic Patients

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SUMMARY To elucidate the pathophysiology of elevated blood pressure in hypercalcemic patients, we studied the plasma concentration of catecholamines and their major metabolites (as an index of sympathetic function) and the blood pressure response to norepinephrine infusion (vascular reactivity) in patients with primary hyperparathyroidism, in patients with primary hypertension, and in normal controls. In addition, we evaluated the hemodynamic response to calcium infusion in normotensive and hypertensive subjects. Plasma levels of both norepinephrine and epinephrine and the metabolites normetanephrine and dihydroxyphenylglycol were significantly higher in the hypercalcemic group than in the other two groups. Norepinephrine infusion increased blood pressure by 8.5 ± 1.4 mm Hg in the control group, by 19 ± 2 mm Hg in the hypercalcemic group and by 29 ± 3 mm Hg in the primary hypertensive group. Infusion of calcium produced a significant rise in both systolic and diastolic blood pressures and in peripheral resistance in the hypertensives, whereas in the normotensive group only systolic blood pressure increased, associated with a rise in cardiac output. We conclude that the observed increased activity of the sympathetic nervous system in hypercalcemia could account for the elevation in blood pressure and the enhanced vascular reactivity could explain the hypertension in some patients with primary hyperparathyroidism. (Hypertension 4: 452-458, 1982)

Key Words • plasma catecholamines • norepinephrine infusion

A n acute increase1, 2 or decrease3, 4 in serum calcium is usually associated with a concordant change in blood pressure. Chronic hypercalcemia also is associated with increased blood pressure,6 and approximately one-third of the patients with primary hyperparathyroidism have hypertension.6, 7 However, the pathogenesis of hypercalcemia-induced hypertension is not known. Since the sympathetic nervous system plays an important role in blood pressure regulation, an abnormality in its function may be present in hypercalcemic states. Experimental studies have indicated that the release of catecholamines is calcium-dependent.5, 9 Increased calcium ion activity may augment the release of catecholamines from both nerve terminals10, 11 and the adrenal gland.10, 12 Also, calcium ions may increase the response of isolated artery to sympathetic stimulation and to catecholamines.13

To elucidate the pathogenesis of hypertension in hypercalcemia, we have evaluated the function of the sympathetic nervous system and vascular reactivity to norepinephrine in patients with primary hyperparathyroidism, primary hypertension, and normotensive subjects. In addition, the hemodynamic change produced by calcium infusion was evaluated in hypertensive and normotensive subjects.

Materials and Methods

The function of the sympathetic nervous system and the blood pressure response to norepinephrine (NE) infusion were evaluated in three groups of subjects: Group 1, 15 patients with primary hyperparathyroidism and normal renal function; Group 2, 12 patients with uncomplicated primary hypertension; and Group 3, 10 normotensive and healthy subjects age matched with previous groups. Patients with manifest atherosclerotic vascular disease, heart failure, or serum creatinine greater than 1.5 mg/dl (normal range, 0.4-1.3 mg/dl) were excluded from these studies.

The diagnosis of primary hypertension was made by history, physical examination, and laboratory proce-
dures including electrocardiogram, chest x-ray, intravenous rapid sequence pyelogram, complete blood count, urinalysis, blood chemistries, and plasma catecholamine determination. The normotensive subjects were healthy employees in this institution. Their health status was evaluated by history, physical examination, and laboratory procedures including electrocardiogram, blood count, urinalysis, and blood chemistries. The clinical characteristics of the studied subjects are included in table 1.

The diagnosis of primary hyperparathyroidism was made in 15 patients on the basis of elevated serum parathyroid hormone (table 2) and abnormal response to an oral calcium load;\textsuperscript{14} in six patients, the diagnosis was confirmed at surgery. Serum total calcium was determined by an automated blood analyzer (normal levels 8.6–10.3 mg/dl), whereas serum ionized calcium was measured potentiometrically using a calcium selective flow-through electrode connected to a digital pH/MW meter (Orion Research Corporation).

Vascular reactivity to NE infusion was determined by the degree of increase in mean arterial pressure (MAP) during the infusion.\textsuperscript{16} The index of reactivity was calculated from the ratio of MAP increase to plasma NE increase at the end of infusion.

The study was approved by the Institutional Human Rights Research Committee, and informed consent was obtained from all subjects. All previous medication was discontinued for at least 2 weeks prior to the testing. None of the hypercalcemics had taken any calcium-reducing medication in the 10 days before testing. The NE infusion technique has been described elsewhere.\textsuperscript{17} After the subject had relaxed for 60 minutes, blood was drawn for determination of basal levels of catecholamines, catecholamine metabolites, and serum levels of calcium, phosphate, magnesium, and electrolytes. Subsequently, NE was infused via an accurate infusion pump (Harvard Apparatus, Millis, Massachusetts) at 0.05 μg/kg/min. over a period of 15 minutes; at the end, another blood sample was obtained.

The hemodynamic response to intravenous (i.v.) calcium was studied in five male hypertensives (mean age, 55 ± 5 years; range, 44–65 years) and in five male normotensives (mean age, 50 ± 4 years; range, 45–60 years). All subjects were admitted to the Clinical Research Center for 3 days, and underwent the calcium infusion studies in the hemodynamic laboratory during the morning hours of the second hospital day, without premedication. The hemodynamic measurements were obtained with standard procedures.\textsuperscript{18} After 30 minutes after insertion of catheters, three sets of arterial pressure and cardiac output measurements were obtained, to serve as control measurements. Then 10% calcium gluconate solution was diluted in 5% dextrose in water and administered via an infusion pump at a rate of 1 ml/min. A total amount of 7–8 mg of elementary calcium per kg of body weight was delivered. During the 2-hour infusion period, pressure and cardiac output measurements were repeated at 15, 60, and 120 minutes.

To determine possible effects on blood pressure of the infusion per se and the laboratory environment, five subjects (three hypertensive and two normotensive) were brought to the hemodynamic laboratory during the morning hours of the third hospital day. An indwelling catheter was inserted into an antecubital vein and 5% dextrose in water was infused at a rate of 1 ml/min over a period of 2 hours. The average blood pressure before the infusion was 136 ± 4/94 ± 4 mm Hg, systolic/diastolic and 142 ± 7/97 ± 4 mm Hg at the end of infusion. The change was not significant.

For measurement of plasma catecholamines and catecholamine metabolites, we used two radioenzymatic assays that have been developed in our laboratory. One assay uses the catechol-0-methyl transferase enzyme and the isotope S-adenosyl-1-methionine-\textsuperscript{3}H, (\textsuperscript{3}H-SAME) to determine levels of noradrenaline, epinephrine, DOPEG, and DOMA simultaneously. Normetanephrine was determined by another radioenzymatic assay that uses the enzyme phenylethanolamine-N-methyl transferase and the \textsuperscript{3}H-SAME. Details of both assays have been described elsewhere.\textsuperscript{13} 18

For statistical analysis, the Student's t test was used to compare the groups, and the paired t test to determine the change within the same group. Correlation coefficients were also determined. Results are expressed as means ± standard error of the mean.

Results

Clinical Characteristics

Tables 1 and 2 include some clinical and laboratory data from the subjects. Age ranges were similar in the three groups: Normotensive subjects, 31–58 years; hypertensive patients, 30–60 years; and hyperparathyroidism patients, 25–63 years. Basal mean pressure of hypertensives, 111 ± 4 mm Hg, was higher than in the other two groups, but was of statistical significance only in comparison to the normotensive mean of 94 ± 2 mm Hg, but not to that of the hyperparathyroidism group, 102 ± 4 mm Hg. The latter group had three patients with a history of labile hypertension, intermittently on therapy, and three patients with sustained hypertension, receiving regular antihypertensive agents. Pertinent data on these six hypertensive patients are as follows: Patient T. B., a 59-year-old man, was a known hypertensive since 1974 and hypercalcemic since 1978. Patient L. G., a 63-year-old woman, had a history of hypertension for 15 years and mild hypercalcemia since 1974. Patient J. R., a 48-year-old woman had a history of labile hypertension for 5 years and sustained hypertension for 1 year; elevated serum calcium had been diagnosed 1 year earlier. Patient D. K., a 24-year-old man, had had a
TABLE 1. Clinical and Laboratory Characteristics of the Population Studied

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>MAP (mm Hg)</th>
<th>Total calcium (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>Albumin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normotensive</td>
<td>10</td>
<td>48 ± 3</td>
<td>6M</td>
<td>94 ± 2</td>
<td>9.3 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>4.3 ± 0.1</td>
</tr>
<tr>
<td>2. Hypertensive</td>
<td>12</td>
<td>49 ± 3</td>
<td>6M</td>
<td>111*</td>
<td>10.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>4.5 ± 0.1</td>
</tr>
<tr>
<td>3. Hypercalcemic</td>
<td>15</td>
<td>50 ± 3.4</td>
<td>7M</td>
<td>102 ± 4</td>
<td>11.2†↑</td>
<td>1.0 ± 0.1</td>
<td>4.0†↑</td>
</tr>
</tbody>
</table>

*Significant at p value less than 0.001 from Group 1.
†Significant at p value less than 0.01 from Group 1.
‡Significant at p value less than 0.01 from Group 2.

MAP = mean arterial pressure; M = male; F = female.

Table 2 shows plasma levels of catecholamines and their major metabolites during the baseline period in all three groups of subjects. In the hypercalcemic group, plasma levels of NE and E were significantly higher than in the normotensive and hypertensive groups.}

Table 3 shows plasma levels of catecholamines and their major metabolites during the baseline period in all three groups of subjects. In the hypercalcemic group, plasma levels of NE and E were significantly higher than in the normotensive and hypertensive groups.
higher than in the normotensive (p < 0.05 for NE and p < 0.02 for E) and the hypertensive (p < 0.02 for NE and p < 0.05 for E) groups. In the hypercalcemic group, however, the six hypertensive patients had higher levels of plasma NE (391 ± 70 vs 175 ± 20, p < 0.05) and E (88 ± 15 vs 52 ± 9 NS) than the rest of the nine hypercalcemics. In the hypercalcemic group, the catecholamine metabolic products of both the deaminated and 0-methylated pathways were higher than in the other two groups, but the difference attained significance from the normotensive group only, and for NMN (p < 0.05) and DOPEG (p < 0.02).

Table 4 includes the change in MAP and plasma NE produced by NE infusion in the three groups of subjects. Although the mean change in NE at the end of infusion was similar in all three groups, the increase in MAP was different. Thus, in the normotensive group, MAP increased by 8.5 ± 1.4 mm Hg; in the hypertensive group, by 29 ± 3 mm Hg; and in the hypercalcemic group, by 19 ± 2 mm Hg. The change in MAP in the hypertensive group was significantly greater than in the normotensive group (p < 0.01). Groups was greater than in the normotensive group (p < 0.01). Because there was some interindividual difference in the extent of the change in plasma NE, we calculated the index of vascular reactivity. Again, both the hypertensive and the hypercalcemic groups had greater vascular reactivity than the normotensive group. In the hypercalcemic group, the six hypertensives had an index of reactivity of 33 ± 7 as against 23.4 ± 3.7 in the rest of the group (NS). The reactivity in both subgroups was greater than in the normotensive group (p < 0.05).

Table 5 summarizes the effect of calcium infusion on intraarterial blood pressure in five hypertensive and five normotensive subjects. In the hypertensive group, at the end of 130 ± 7 minutes of infusion, serum ionic calcium increased from 3.8 ± 0.2 to 5.0 ± 0.4 mg/100 ml (p < 0.05), but only the systolic blood pressure increased significantly (p < 0.005). The extent of the change in systolic and diastolic blood pressure was 33 ± 4 and 22 ± 5 mm Hg, respectively, in the hypertensive group, and 20 ± 2 and 7 ± 3 mm Hg in the normotensive group. The difference between the two groups was significant for systolic blood pressure only (p < 0.05). In both groups, infusion of calcium did not produce any change in hematocrit or in serum sodium, potassium, chloride, bicarbonate, and magnesium levels.

The mechanism by which MAP increased during calcium infusion was different between the two groups (table 6). In the hypertensive group, cardiac output did not change; therefore, the increase in blood pressure was due to an increase in peripheral resistance. In the normotensive group, however, there was a significant increase in cardiac output, from 4.4 ± 0.5 to 5. ± 0.3 liters/min (p < 0.05).

Discussion

This study shows that an acute increase in serum calcium was associated with a significant increase in both systolic and diastolic blood pressures in hypertensive patients, but in only systolic pressure in normotensives. In addition, the mechanism by which

<table>
<thead>
<tr>
<th>Table 5. Effect of Calcium Infusion on Blood Pressure in Normotensive and Hypertensive Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td><strong>Control period</strong></td>
</tr>
<tr>
<td>SBP</td>
</tr>
<tr>
<td>1. Normotensive</td>
</tr>
<tr>
<td>± 8</td>
</tr>
<tr>
<td>2. Hypertensive</td>
</tr>
<tr>
<td>± 7</td>
</tr>
<tr>
<td>*Change was significant at p &lt; 0.05.</td>
</tr>
<tr>
<td>†Change was significant at p &lt; 0.02.</td>
</tr>
<tr>
<td>††Change was significant at p &lt; 0.005.</td>
</tr>
<tr>
<td>SBP = systolic blood pressure; DBP = diastolic blood pressure.</td>
</tr>
</tbody>
</table>
blood pressure changed was also different. In the hypertensives, peripheral resistance increased whereas in normotensives cardiac output increased significantly. In one previous study of the cardiovascular effects of calcium infusion in humans, \(^{44}\) cardiac output was increased, whereas in two other studies \(^{18, 46}\) total peripheral resistance was increased. Differences in protocols and/or selected subjects may account for these divergent results. Overbeck et al. \(^{50}\) infused calcium into the brachial artery without producing a change in systemic blood calcium or blood pressure and found that the vasoconstrictor response to calcium was similar in normotensive and hypertensive men.

Pang et al. \(^{52, 61}\) and other investigators \(^{42, 53}\) have shown that administration of parathyroid hormone (PTH) and its N-terminal 1–34 fragment is associated with a fall in blood pressure and an increase in blood flow of many vascular beds. Furthermore, vitro studies demonstrated that PTH relaxed the aortas of both rabbit and rat. \(^{54, 55}\) Since infusion of calcium is associated with a reciprocal decrease in PTH, \(^*\) the vasopressor effect of calcium is counteracted by the vasodepressor action of PTH. In a recent study by McCarron et al., \(^{44}\) infusion of calcium in 13 renal transplant recipients (with persistent hyperparathyroidism and many with hypertension) produced a significantly greater increase in systolic blood pressure and a significantly greater suppression of PTH than in a group of seven controls. These investigators postulated that the blood pressure response to transient hypercalcemia is more dependent on PTH suppression than on levels of calcium. In our calcium infusion studies, since levels of PTH were not measured we cannot rule out the probability that the greater blood pressure response of hypertensives may be related to an enhanced suppression of PTH in this group than the controls.

Several studies have indicated that calcium has an important effect on systemic blood pressure. In vivo, local infusion of calcium evokes vasoconstriction. \(^{51}\) In the dog, calcium vasoconstriction has been demonstrated in various vascular beds, including the limb, \(^{21, 22}\) the heart, \(^{24}\) and the kidney. \(^{29}\) Whereas slow infusion of calcium in the dog produces bradycardia with little change in MAP, \(^{26, 61}\) more rapid administration of calcium raises blood pressure in the dog \(^{6, 27}\) and cat. \(^{28}\) Increased cardiac output, \(^{25}\) total peripheral resistance, \(^{7, 30}\) and regional resistance \(^{48}\) have been reported. In humans, intravenous infusion of 15 mg of calcium per kilogram of body weight over a 4-hour period resulted in a rise of at least 30 mm Hg in 47% of 19 patients of Moore and Smith, \(^{30}\) whereas short infusions have produced an increased myocardial contractility with little change in blood pressure. \(^{21}\)

Both an acute and chronic rise in serum calcium is associated with an elevation in blood pressure that may not necessarily attain hypertensive levels. \(^{1, 8}\) Nevertheless, hypertension is more common in patients with primary hyperparathyroidism than in the general population, \(^*\) yet the underlying pathophysiology is not known. Experiments in vitro have shown that calcium exerts a direct, but biphasic, effect on the contractile response of vascular smooth muscle. \(^{44, 46}\) In acute hypercalcemia, a direct effect of calcium is the likely underlying factor for the hypertension. In chronic hypercalcemia, however, hypertension is not a consistent finding, so that factors other than a direct effect of calcium probably participate in the pathophysiology of hypertension.

In patients with long-standing primary hyperparathyroidism, the hypertension is considered to be secondary to renal damage resulting from nephrocalcinosis, nephrolithiasis, and urinary tract infection. Hellström et al. \(^*\) reported a striking correlation between the extent of renal damage in hyperparathyroidism and the severity of hypertension. However, in recent years, the determination of serum calcium as part of routine screening blood studies in all patients makes possible the discovery of primary hyperparathyroidism before symptoms develop. In the vast majority of these patients, renal function is normal, yet hypertension was present in 19 out of 52 hypercalcemic patients studied by Britton et al. \(^{32}\) Christensson and associates \(^*\) reported that both systolic and diastolic blood pressures were significantly greater in 68 patients with primary hyperparathyroidism than in a similar number of sex- and age-matched normocalcemic subjects, and that this difference was not related to impaired renal function, family history of hypertension, or body weight. McCarron et al. \(^{33}\) in a preliminary study have reported

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**Table 6. Effect of Calcium Infusion on Cardiac Output, Heart Rate, and Total Peripheral Resistance in Normotensive and Hypertensive Subjects**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiac output (liter/min)</th>
<th>Heart rate (beats/min)</th>
<th>Total peripheral resistance (dynes/sec cm(^{-2}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>1. Normotensive</td>
<td>4.4</td>
<td>±0.5</td>
<td>5.1</td>
</tr>
<tr>
<td>2. Hypertensive</td>
<td>4.1</td>
<td>±0.34</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*Change was significant at \( p < 0.05 \).
†Change was significant at \( p < 0.05 \) between the two groups.
C = control period; I = infusion period.
that patients with primary hypertension demonstrated a relative hypercalciuria and increased levels of serum parathyroid hormone. These findings suggest that parathyroid gland function may be enhanced in primary hypertension, and the prevalence of hypertension in patients with hyperparathyroidism may represent a continuum that begins with hypertension and a kidney leak of calcium leading to the pathophysiological presentation of hyperparathyroidism.

In our present study, the plasma concentrations of both norepinephrine and epinephrine were significantly higher in the hypercalcemic groups than in the normocalcemic groups of both the normotensive \((p < 0.05\) for NE and \(p < 0.02\) for E) and primary hypertensive subjects \((p < 0.02\) for NE and \(p < 0.05\) for E). In addition, the elevation in plasma catecholamines was more pronounced in the six patients with hypercalcemia and hypertension than in the rest of the group. Experimental evidence indicates that the release of catecholamines is calcium-dependent, and increased calcium ion activity may augment the release of catecholamines from nerve terminals and the adrenal gland. Therefore, the increased levels of catecholamines observed in our hypercalcemic subjects should indicate increased catecholamine release and possibly increased amounts of catecholamines at postsynaptic receptors, resulting in elevation of blood pressure, though not necessarily hypertension.

In a recent study in humans, infusion of calcium over a period of 3 hours produced an early and progressive increase in blood pressure, and a late elevation in the concentrations of both plasma epinephrine and norepinephrine. These findings suggest that initial elevation of blood pressure results from a direct effect of calcium on blood vessels, whereas later, catecholamines released by calcium may contribute to the sustained pressure elevation.

In our present study, the catecholamine metabolites were also elevated in patients with hypercalcemia. Both the 0-methylated metabolite of norepinephrine, normetanephrine, and the deaminated metabolite DOPEG were significantly higher in the plasma of patients with primary hyperparathyroidism than in the normotensive group (table 3). In our patients with normal renal function, the increased concentrations of plasma catecholamine metabolites should indicate increased catecholamine release and metabolism.

The contribution of the several metabolic pathways to the metabolism of NE in peripheral tissues differs in different species. Studies in whole animals show that overflow of NE released from sympathetic nerve endings is mainly metabolized by 0-methylation, whereas NE within nerve endings is predominately deaminated. Experimental evidence indicates that normetanephrine is a major extraneuronal metabolite of NE. Since the 0-methylating enzyme, catechol-0-methyltransferase, is almost exclusively located in extraneuronal tissues, normetanephrine is considered to be only an extraneuronal metabolite. Therefore, the increased levels of normetanephrine observed in the hypercalcemic patients should indicate increased amounts of NE at postsynaptic receptors.

Our patients with primary hypertension demonstrated a greater blood pressure increase in response to NE infusion than the other two groups \((p < 0.001\) from the normotensives and \(p < 0.05\) from the hypercalcemics), whereas their calculated index of vascular reactivity was greater than the normotensive group only \((p < 0.01)\). Enhanced vascular reactivity in patients with primary hypertension has been reported in previous studies in which, however, the plasma concentration of NE was not determined. Thus, the variability of the relationship of drug dose to plasma concentration was ignored. In our hypercalcemic group, both the increase in MAP and the index of vascular reactivity to NE was significantly elevated. This enhanced vascular response was most pronounced in the six hypercalcemic patients with hypertension. Experimental evidence indicates that calcium ions are not only important for arterial smooth muscle contraction but may increase both the response of isolated artery to sympathetic stimulation and catecholamines. Several investigators have reported that isolated small arterial segments obtained from DOCA-hypertensive and renal hypertensive rats also demonstrated hyperresponsiveness to catecholamines. Bohr and Sittrin have suggested that the increased responsiveness in hypertensives might be attributable to increased vascular smooth muscle membrane permeability to calcium ions. Tobian and Chesley reported an increased calcium content of arterioles from rats with one-kidney Goldblatt hypertension, whereas Hinke found increased calcium content in segments of the ventral tail artery from DOCA-hypertensive rats.

In conclusion, our studies have demonstrated that some patients with primary hyperparathyroidism have enhanced sympathetic activity and increased vascular reactivity to NE. It is tempting to speculate that the former abnormality could account for the elevation of blood pressure in hypercalcemia, whereas the latter may be responsible for the observed hypertension in some patients with primary hyperparathyroidism.

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