

Effects of Calcium Infusion on Blood Pressure in Hypertensive and Normotensive Humans

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SUMMARY Disorders of calcium and parathyroid hormone homeostasis have been reported in subjects with essential hypertension. In many of these studies, dietary intakes of sodium and calcium were not carefully controlled. The present study was designed to compare calcium and parathyroid hormone homeostasis in normal and hypertensive subjects on controlled dietary sodium and calcium intakes and to examine the impact of dietary sodium loading on hemodynamic and metabolic responses to infused calcium. Seven subjects with essential hypertension and seven age-matched and sex-matched controls were studied while consuming a standard diet containing 600 mg of elemental calcium. Each subject was studied while consuming 10, 160, and 510 mEq of sodium per day, before, during, and after a 3-hour calcium infusion (3.75 mg/kg/hr). Before calcium infusion, hypertensive subjects had increased urinary cyclic adenosine 3',5'-monophosphate excretion independent of sodium intake ($p < 0.05$). Urinary potassium excretion was greater in normotensive than in hypertensive subjects ($p = 0.002$). At baseline, dietary sodium intake had no effect on systolic, diastolic, or mean arterial pressure. During calcium infusion, systolic pressure increased in both groups, whereas diastolic pressure increased only when dietary sodium content was high and mean arterial pressure increased only in hypertensive subjects ($p = 0.007$). Together, these data provide evidence for interactions between dietary sodium intake and the cardiovascular response to calcium. They confirm that hypertensive subjects exhibit enhanced parathyroid gland function even when dietary factors are controlled, and they suggest that these subjects are more sensitive to the cardiovascular effects of short-term calcium infusion. (Hypertension 8: 497-505, 1986)

KEY WORDS • parathyroid hormone • blood pressure • cyclic adenosine monophosphate

CALCIUM metabolism may be abnormal in patients with essential hypertension and in several experimental models of the disease. Disturbances that have been described in humans include increased urinary calcium excretion,^{1,2} enhanced parathyroid gland activity,^{1,2} and reduced levels of serum ionized calcium.^{3,4} In several experimental models of hypertension, similar abnormalities have been identified,^{5,6} including increased rates of parathyroid hor-

mone (PTH) secretion^{5,6} and alterations of membrane calcium sensitivity,⁷ perhaps secondary to disordered membrane calcium binding.⁸

Most clinical reports of disordered calcium homeostasis have neglected careful control of several important determinants of calcium metabolism. Dietary intake of calcium or sodium may influence renal excretion of the other ion,^{6,9} and each may participate in blood pressure control, either directly or through their diverse interactions.⁹⁻¹¹ Recent reports highlight the major effects of changes in dietary sodium chloride intake on renal calcium excretion^{9,11} and suggest that some sodium chloride-dependent effects may be mediated directly by changes in systemic calcium balance. The present experiments were designed to compare the hemodynamic and metabolic responses to short-term calcium infusion in normal subjects and in subjects with essential hypertension. Calcium infusion was performed while subjects consumed diets that differed in sodium content to investigate interactions between dietary sodium intake and the response to calcium.

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Subjects and Methods

Seven subjects with essential hypertension and seven age-matched and sex-matched control subjects participated in the study. All subjects were white. Criteria for entry of hypertensive subjects included documented ambulatory blood pressures in excess of 140/90 mm Hg on at least three occasions and the absence of other chronic diseases requiring medical therapy. Hypertensive subjects had previously undergone specific investigations designed to rule out secondary causes of hypertension, and each carried the diagnosis of essential hypertension. At the time of entry into the study, 1) routine urinalysis results showed less than 1+ proteinuria and were negative for occult blood (Multistix, Ames, Elkhart, IN, USA) and 2) automated chemistry screen results (SMAC, Technicon, Tarrytown, NY, USA) showed normal serum potassium, creatinine, total calcium, and phosphorus levels. Table 1 compares characteristics of the two groups. Although hypertensive subjects tended to weigh more than control subjects, this difference was not significant ($t = 1.16$ by unpaired t test).

Most hypertensive subjects were taking oral antihypertensive medications before entry into the study. Medications were withdrawn approximately 2 weeks before the study began. Although at least 10 drug-free days were required before beginning the study, the possibility that some of the observed differences were due to residual drug effects cannot be excluded. A general outline of the experimental protocol is shown in Figure 1. The study was divided into three parts and lasted 13 days. On Day 1, the subject received dietary instruction and was given a dietary log book in which to record daily food consumption. The daily diet contained 10 mEq of sodium and approximately 600 mg of elemental calcium, a portion of which was administered as calcium carbonate. The subject consumed this diet throughout the study. A 24-hour urine sample was collected on the fifth day and was analyzed for sodium, calcium, and creatinine as a check on dietary adherence. On the fifth day, the subject entered the Clinical Research Center for Test Day 1. After the test day protocol (described below) had been completed, an additional 150 mEq of sodium per day (in a preweighed package) was added to the initial diet. The subject then ingested the same diet with the additional

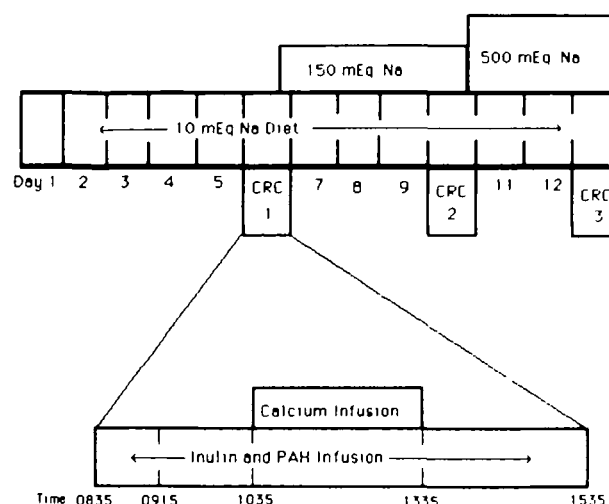


FIGURE 1. Experimental protocol. Each subject consumed the same diet throughout the 13 study days. Sodium was supplemented in preweighed packages. On the test days, inulin and p-aminohippurate (PAH) clearance measurements were begun at 0915. CRC = Clinical Research Center.

sodium for the next 4 days. A 24-hour urine sample was collected on the third day (Study Day 9) and analyzed for sodium, creatinine, and calcium. The subject entered the Clinical Research Center on Study Day 10 for Test Day 2. Following completion of the test day protocol, dietary sodium was increased to 510 mEq/day. On the twelfth day, a 24-hour urine sample was collected and analyzed for sodium, creatinine, and calcium. On Day 13, the subject entered the Clinical Research Center for the last of 3 test days.

The protocol during each of the 3 test days was identical. Two intravenous catheters were placed, one for infusions and one for drawing blood. An oral water load (750 ml) was administered to ensure adequate urine flow, and loading doses of p-aminohippurate (PAH), 6 mg/kg, and inulin, 50 mg/kg, were given intravenously during a 5-minute period. Following this loading dose, dextrose in water, 50 g/L, with PAH, 2 g/L, and inulin, 5 g/L, were infused at 250 ml/hour. After 45 minutes had elapsed to allow the attainment of steady state conditions, clearance measurements were begun. Urine samples were collected every 20 minutes, blood samples were obtained at the midpoint of each 20-minute cycle. This procedure provided a continuous series of 20-minute clearance periods. Blood pressure, pulse, and respiratory rate were measured every 20 minutes during the infusions. Two hours after clearance measurements had begun, an infusion of elemental calcium as gluconate was initiated at a rate of 3.75 mg/kg/hr and continued for 3 hours. At the end of this period, calcium was removed and inulin and PAH infusion continued for 2 more hours. Thus, clearances were measured continuously for 7 hours.

Blood pressures were measured by standard sphygmomanometry. Systolic pressure was defined as the

TABLE 1. Subject Characteristics at Time of Entry into Study

Characteristic	Hypertensive	Normotensive
Sex (M/F)	4:3	4:3
Age (yr)	42 ± 4.5	42 ± 4.5
Blood pressure (mm Hg)		
Systolic	156 ± 2.8	118 ± 4.2*
Diastolic	100 ± 3.5	72 ± 2.8*
Weight (kg)	80 ± 6.6	70 ± 4.8
Creatinine (mg/dl)	1.0 ± 0.05	0.9 ± 0.07

Values are means ± SE.

* $p < 0.001$, compared with values in hypertensive subjects.

point at which the Korotkoff sounds first appeared, diastolic pressure was defined as the point at which these sounds disappeared. Serum samples were analyzed for sodium, potassium (Autoanalyzer), ionized calcium (Clin ± Ion, Menlo Park, CA, USA), inulin,¹² and PAH (by photometry at 540 nm following coupling with diazotized *N*-[1-naphthyl]ethylenediamine dihydrochloride). Urine was analyzed for sodium, potassium, calcium, PO₄ (Autoanalyzer), cyclic adenosine 3',5'-monophosphate (cAMP; New England Nuclear, Boston, MA, USA), and inulin and PAH (as above). Clearances of inulin and PAH were calculated as $[U]_x \times V/[P]_x$, where $[U]_x$ is the concentration of inulin or PAH in the urine, V is the volume flow rate, and $[P]_x$ is the concentration of inulin or PAH in the plasma measured at the midpoint of the urine collection. Fractional ion excretion was calculated as

$$\frac{[U]_i}{[P]_i} \times \frac{[P]_{IN}}{[U]_{IN}} \times 100$$

where $[U]_i$ is the urinary ion concentration, $[P]_i$ is the plasma ion concentration, and $[P]_{IN}$ and $[U]_{IN}$ are the inulin concentrations in plasma and urine respectively.

Baseline data were analyzed using a two-way analysis of variance (ANOVA) and unpaired *t* test. Statistical analysis of the calcium infusion data employed a multivariate analysis of variance and covariance with repeated-measure design (BMDP and SAS programs). With the use of this approach, variances could be attributed to group effects (hypertensive vs normal subjects), time effects (effects of calcium infusion), and diet effects (effects of dietary sodium intake) as well as to interactions between these variables. To assess changes in blood pressure, baseline measurements (before calcium infusion) were taken as covariates. Statistical significance was accepted at the *p* less than 0.05 level.

This protocol was approved by the Human Investigations Committee of the Oregon Health Sciences University. Each subject gave voluntary informed consent before participation.

Results

Baseline data obtained before entry into the study are shown in Table 1. The normotensive and hypertensive subjects were well matched for age, sex, baseline creatinine levels, and weight. Subjects were judged to have adhered to the dietary regimens by two criteria. First, food diaries indicated that each subject remained within the dietary guidelines. Second, baseline 24-hour urinary sodium excretion increased when dietary sodium intake was raised.

Blood pressures are shown in Table 2. As expected, before calcium infusion, systolic and diastolic pressure and mean arterial pressure (MAP) were higher in the hypertensive subjects than in the normotensive control group. During the study, dietary sodium intake did not alter baseline blood pressure significantly in either group (diet effect, *p* = 0.827 by ANOVA; see Table 2). Systolic pressure rose significantly in response to calcium infusion in both groups (time effect, *p* < 0.001 by ANOVA; Figure 2). Dietary sodium intake altered the relation between calcium infusion and systolic pressure in both groups (diet/time effects, *p* < 0.05 by ANOVA); however, dietary sodium affected the pressor response to calcium in hypertensive subjects differently than in normotensive subjects (diet/time/group effect, *p* < 0.02 by ANOVA). Specifically, normotensive subjects increased systolic pressure in response to calcium infusion only during the higher sodium diet periods (160 and 510 mEq/day), whereas hypertensive subjects were sensitive to the cardiovascular effects of calcium regardless of sodium intake. There was no correlation between changes in serum ionized calcium and systolic pressure in either group (Figure 3).

Diastolic pressure responses are shown in Table 2 and Figure 4. Although calcium infusion did not alter diastolic pressure significantly when all dietary conditions were considered together (time effect, *p* = 0.212 by ANOVA), calcium infusion led to increases in diastolic pressure during certain dietary sodium periods. Calcium infusion did not alter diastolic pressure in either group during low sodium intake, but diastolic pressure did increase (diet/time effect, *p* = 0.037 by ANOVA) when dietary sodium was greater. The inter-

TABLE 2. Effects of Dietary Sodium Content on Systolic, Diastolic, and Mean Arterial Pressure Response to Infused Calcium

Variable	Low Na ⁺ (10 mEq/day)			Medium Na ⁺ (260 mEq/day)			High Na ⁺ (510 mEq/day)		
	B	D	A	B	D	A	B	D	A
Systolic BP									
Normotensive	117 ± 5.9	114 ± 3.3	114 ± 6.1	113 ± 5.0	123 ± 4.0	120 ± 6.8	111 ± 4.5	118 ± 3.7	122 ± 5.8
Hypertensive	141 ± 3.1	155 ± 4.0	144 ± 5.7	139 ± 5.4	149 ± 3.2	150 ± 6.6	145 ± 6.6	154 ± 5.2	158 ± 9.3
Diastolic BP									
Normotensive	73 ± 5.1	69 ± 1.6	69 ± 3.1	69 ± 2.8	70 ± 2.0	71 ± 3.7	69 ± 4.4	71 ± 2.1	71 ± 4.3
Hypertensive	91 ± 1.5	93 ± 2.4	91 ± 4.3	87 ± 2.8	92 ± 2.2	95 ± 5.6	88 ± 5.1	94 ± 4.0	97 ± 7.0
MAP									
Normotensive	88 ± 4.2	84 ± 2.0	84 ± 2.8	83 ± 2.8	87 ± 2.4	87 ± 3.1	83 ± 3.2	87 ± 2.5	88 ± 3.3
Hypertensive	108 ± 1.4	114 ± 2.7	109 ± 5.4	104 ± 3.5	111 ± 2.7	114 ± 5.7	107 ± 5.0	113 ± 4.7	118 ± 7.4

Values are means ± SE before (B), during (D), and after (A) calcium infusion. BP = blood pressure; MAP = mean arterial pressure.

FIGURE 2. Effects of calcium infusion on systolic blood pressure. Measurements were made immediately before, during (at 1, 2, and 3 hours), and 1 hour after calcium infusion. Statistics are shown in Table 2.

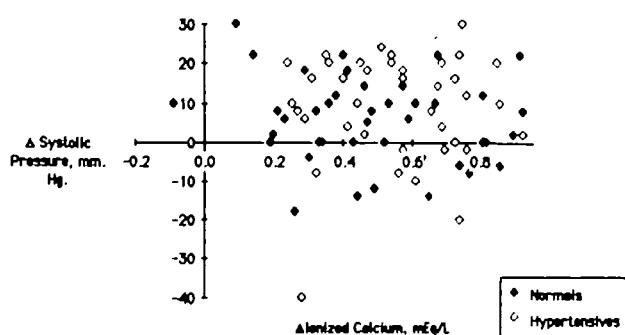
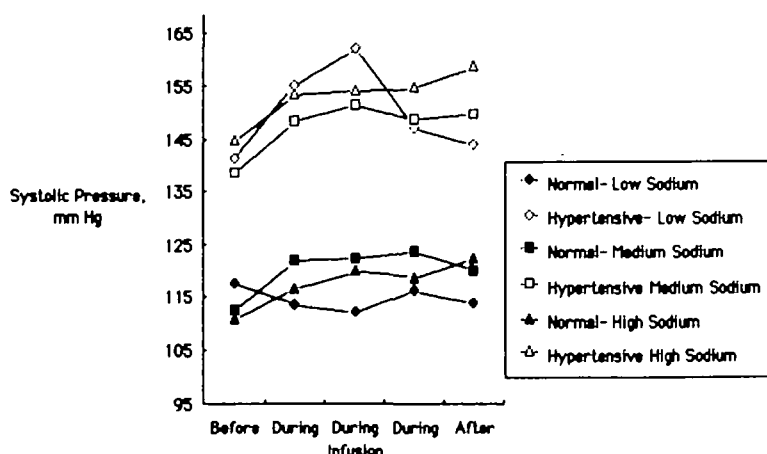


FIGURE 3. Comparison of changes in systolic pressure and serum ionized calcium concentration.

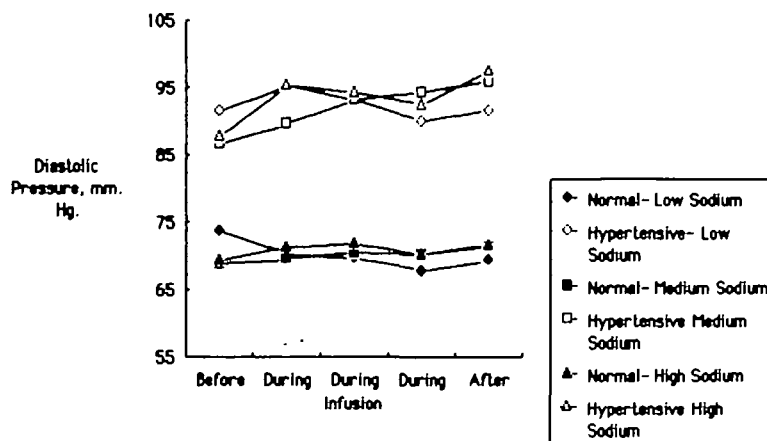
action between diet and calcium infusion could not be shown to be different between groups (diet/time/group effect, $p = 0.935$ by ANOVA).

The effects of calcium infusion on MAP are shown in Table 2 and Figure 5. During the infusion of calcium in hypertensive subjects, MAP rose significantly and independently of dietary sodium intake, whereas in normal control subjects calcium infusion had no significant effect on MAP (group effect, $p = 0.007$ by

ANOVA). Of further note is the temporal dissociation between blood pressure and serum calcium concentration. In the hypertensive subjects, MAP rose during calcium infusion as serum calcium levels increased but MAP remained elevated as serum calcium levels began to fall during the recovery period.

Inulin and PAH clearances and fractional excretion rates for sodium and potassium are shown in Table 3. Note that all fractional excretion rates were measured after the start of diuresis. Inulin clearance (overall mean, 105 ± 7.7 vs 105 ± 7.4 ml/min) and PAH clearance (overall mean, 544 ± 45.6 vs 473 ± 35.6 ml/min) were similar in normotensive and hypertensive subjects, respectively, and were not altered significantly by sodium intake. Although, as expected, fractional sodium excretion was influenced significantly by dietary sodium intake (diet effect, $p < 0.001$), overall mean fractional sodium excretion was similar in normotensive and hypertensive subjects (2 ± 0.4 vs $2 \pm 0.6\%$, respectively; group effect, $p = 0.618$). Fractional potassium excretion, however, was significantly higher in normal than in hypertensive subjects (overall mean before calcium infusion, 32 ± 0.4 vs $21 \pm 0.3\%$, respectively; group effect, $p = 0.002$). Neither inulin nor PAH clearance was affected significantly by calcium infusion in either group. Increasing dietary sodium intake tended to increase PAH clear-

FIGURE 4. Effects of calcium infusion on diastolic pressure. Measurements were made immediately before, during (at 1, 2, and 3 hours), and 1 hour after calcium infusion. Statistics are shown in Table 2.



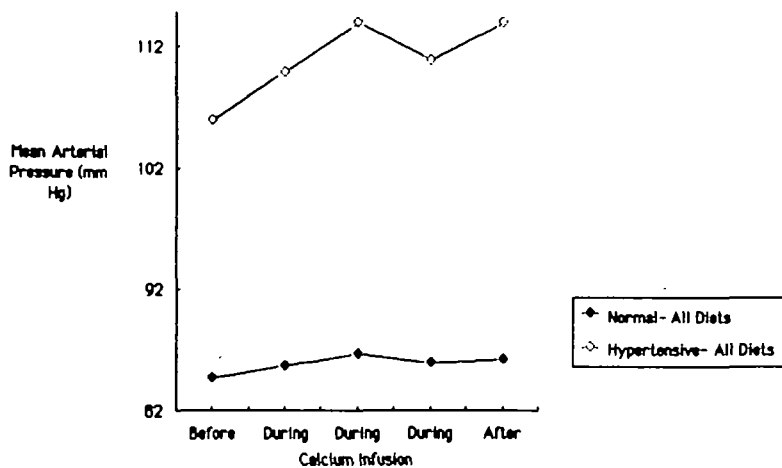


FIGURE 5. Effects of calcium infusion on mean arterial pressure (calculated as diastolic pressure + $1/3(\text{systolic} - \text{diastolic pressure})$). Measurements were made immediately before, during (at 1, 2, and 3 hours), and 1 hour after calcium infusion. Statistics are shown in Table 2.

ance in normal but not in hypertensive subjects, although this difference did not reach statistical significance (diet/group effect, $p = 0.064$). Fractional sodium excretion was increased by calcium infusion (time effect $p < 0.001$ by ANOVA) and by increased dietary sodium intake (diet effect, $p < 0.001$ by ANOVA). Calcium infusion had no effect on fractional excretion of potassium ($p = 0.925$ by ANOVA), although fractional potassium excretion remained higher in normotensive than in hypertensive subjects (group effect, $p = 0.023$ by ANOVA).

Serum ionized calcium, fractional calcium excretion, and urinary cAMP excretion are shown in Table 4. Serum ionized calcium concentration was similar in normotensive and hypertensive subjects (overall mean before calcium infusion, 2.1 ± 0.38 vs 2.1 ± 0.34 mEq/dl, respectively; group effect, $p = 0.661$). Fractional calcium excretion tended to be elevated in hypertensive subjects (6 ± 1.1 vs 4 ± 0.7 in normotensive subjects), but this effect was not significant. Urinary cAMP excretion at baseline (Figure 6) was higher in hypertensive than in normotensive subjects

(5.2 ± 0.52 vs 3.0 ± 0.64 nmol/dl of glomerular filtration rate; $p < 0.05$). Calcium infusion in both groups significantly increased serum calcium levels from baseline regardless of the sodium content of the diet (time effect, $p < 0.001$ by ANOVA). Fractional excretion of calcium also increased significantly during the infusion (time effect, $p < 0.001$ by ANOVA). Conversely, calcium infusion significantly reduced urinary cAMP excretion (time effect, $p = 0.003$ by ANOVA) in both groups.

Discussion

The present study was designed to compare hemodynamic and metabolic responses to short-term calcium infusion in hypertensive and normotensive subjects and to assess the influence of dietary sodium intake on the response to administered calcium. The results show that subjects with essential hypertension excreted more urinary cAMP than did normal subjects even when dietary sodium and calcium intake were controlled and that dietary sodium chloride intake al-

TABLE 3. Effects of Calcium Infusion on Fractional Sodium and Potassium Excretion and Inulin and p-Aminohippurate Clearance

Variable	Low Na ⁺ (10 mEq/day)			Medium Na ⁺ (260 mEq/day)			High Na ⁺ (510 mEq/day)		
	B	D	A	B	D	A	B	D	A
FE_{Na}									
Normotensive	1 ± 0.2	2 ± 0.5	1 ± 0.2	2 ± 0.6	6 ± 0.9	5 ± 1.7	3 ± 0.7	6 ± 1.6	4 ± 0.9
Hypertensive	1 ± 0.2	2 ± 0.4	1 ± 0.4	2 ± 0.9	5 ± 1.1	3 ± 0.8	5 ± 1.2	7 ± 2.1	3 ± 0.9
FE_K									
Normotensive	37 ± 6.2	31 ± 7.8	35 ± 4.9	26 ± 6.1	32 ± 6.3	34 ± 5.4	32 ± 7.4	40 ± 9.9	32 ± 9.4
Hypertensive	24 ± 6.2	16 ± 2.6	18 ± 3.0	16 ± 5.7	19 ± 2.9	25 ± 3.7	22 ± 3.6	18 ± 5.6	18 ± 3.1
C_{IN}									
Normotensive	100 ± 5.1	88 ± 2.9	88 ± 7.3	98 ± 11.0	96 ± 9.3	86 ± 11.5	101 ± 10.4	95 ± 18.0	85 ± 12.7
Hypertensive	96 ± 9.3	113 ± 16.1	103 ± 16.3	111 ± 16.3	92 ± 11.9	93 ± 9.6	93 ± 12.6	98 ± 15.1	108 ± 14.7
C_{PAH}									
Normotensive	445 ± 53.7	494 ± 34.2	481 ± 42.7	617 ± 105.0	596 ± 72.6	502 ± 42.4	571 ± 65.1	625 ± 98.1	492 ± 88.8
Hypertensive	479 ± 59.4	614 ± 125.4	479 ± 68.0	514 ± 70.7	431 ± 75.6	425 ± 68.5	426 ± 59.0	483 ± 100.0	487 ± 71.0

Values are means ± SE before (B), during (D), and after (A) calcium infusion. FE_{Na} = fractional excretion of sodium; FE_K = fractional excretion of potassium; C_{IN} = inulin clearance; C_{PAH} = p-aminohippurate clearance.

TABLE 4. *Effects of Calcium Infusion on Serum Ionized Calcium Concentration, Fractional Calcium Excretion, and Urinary cAMP Excretion*

Variable	Low Na ⁺ (10 mEq/day)			Medium Na ⁺ (260 mEq/day)			High Na ⁺ (510 mEq/day)		
	B	D	A	B	D	A	B	D	A
Serum Ca ²⁺ (mEq/L)									
Normotensive	2.1±0.14	2.7±0.13	2.5±0.08	2.2±0.04	2.7±0.10	2.5±0.10	2.1±0.05	2.8±0.10	2.5±0.07
Hypertensive	2.1±0.06	2.8±0.11	2.6±0.06	2.1±0.05	2.8±0.07	2.5±0.08	2.1±0.07	2.8±0.09	2.6±0.07
FE _{Ca}									
Normotensive	4±0.9	17±3.9	20±7.8	5±1.6	25±6.0	23±4.6	3±0.8	26±5.5	24±8.2
Hypertensive	4±1.4	17±2.9	13±1.9	7±2.3	19±6.4	19±3.7	5±2.1	28±8.0	16±3.0
U _{cAMP} (nmol/dl GFR)									
Normotensive	3.0±0.64	2.1±0.75	—	3.6±1.31	1.7±0.81	—	2.3±0.98	1.7±0.46	—
Hypertensive	5.2±0.52	2.5±0.70	—	4.7±1.25	2.4±1.14	—	4.2±1.02	2.2±0.97	—

Values are means ± SE before (B), during (D), and after (A) calcium infusion. FE_{Ca} = fractional excretion of calcium; U_{cAMP} = urinary cAMP excretion; GFR = glomerular filtration rate.

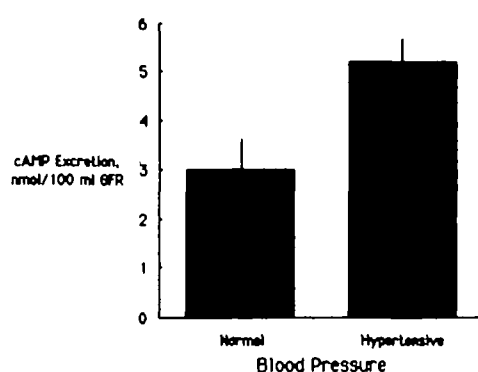


FIGURE 6. *Urinary excretion rate of cAMP in normal and hypertensive subjects before calcium infusion ($p < 0.05$). GFR = glomerular filtration rate.*

tered the cardiovascular response to infused calcium. Hypertensive subjects were also more sensitive to the acute effects of calcium on blood pressure than were normal subjects. Together, these and other abnormalities of sodium and calcium handling may contribute to the pathogenesis of essential hypertension.

Several clear differences in calcium and PTH homeostasis between normal and hypertensive subjects were evident before calcium infusion. Hypertensive subjects excreted more urinary cAMP per deciliter of glomerular filtration rate at baseline (see Table 4). Urinary cAMP excretion reflects the level of parathyroid activity¹³; the rapid suppression of cAMP excretion observed during calcium infusion supports the value of this measure in the present study. Enhanced parathyroid activity has been described in patients with essential hypertension^{1, 2, 14} and in rats with spontaneous hypertension.^{5, 6} Although the cause is unknown, it may be related to increased urinary calcium excretion in this group. We¹ and others² have observed increased rates of urinary calcium excretion in patients with essential hypertension under nonstimulated conditions. Hypertensive subjects tended to excrete more calcium

before infusion than did controls in the present study, but this did not reach statistical significance.

Whereas some larger studies have shown lower levels of serum ionized calcium in subjects with essential hypertension compared with normotensive controls, the present results showed no clear difference. A possible cause for this lack of significant difference is our use of controlled dietary sodium and calcium intake. The controlled dietary conditions, although of relatively brief duration, may have minimized differences in serum ionized calcium, since hypertensive subjects have been reported to consume less dietary calcium than do normal subjects¹⁵ on ad libitum dietary intake. It also seems likely, however, that sample size limited our ability to demonstrate previously described abnormalities. Whether longer term control of dietary sodium and calcium intake would have attenuated or abolished the observed differences in urinary cAMP excretion cannot be addressed by the current data.

As expected, calcium infusion markedly increased serum ionized calcium concentration and urinary calcium excretion and decreased urinary cAMP excretion. Responses in both groups were quite similar in the magnitude of the increases in serum calcium and in urinary responses. Strazzullo et al.² reported that urinary calcium excretion remained higher in patients with essential hypertension than in normal subjects during short-term calcium infusion. In that study, hypertensive subjects excreted more calcium than did normal subjects at every level of serum calcium. In the present experiments, we did not find that hypertensive subjects excreted more calcium during the infusion. The reason for the differences between studies is not clear. Fractional sodium excretion also increased during the calcium infusion in the present study. When administered acutely, calcium is natriuretic,¹⁶ which might cause marked volume depletion during a 3-hour infusion.¹⁷ We could not, however, find significant changes in either inulin or PAH clearance during or after the calcium infusion period.

Increased dietary sodium chloride intake expanded extracellular fluid volume in both normal and hyper-

tensive subjects, as indicated by increased urinary sodium excretion. There was no significant effect of dietary sodium chloride on blood pressure before calcium infusion in either group. Some patients with essential hypertension are especially sensitive to the effects of dietary salt.¹⁸ Many others, and most subjects with normal blood pressure, demonstrate small increases in systolic and diastolic pressure when they ingest extremely large quantities of sodium (as much as twice the maximal sodium intake employed in the present study).¹⁹ The minimal effects of dietary sodium observed in the present study are compatible with the minimal effects of dietary sodium loading previously described,¹⁹ although a longer duration of reduced or elevated sodium consumption might have affected blood pressure significantly. Increasing dietary sodium intake, when consumed as sodium chloride, can induce a state of negative calcium balance by increasing urinary calcium excretion.⁹

Some hemodynamic changes often directly attributed to altered sodium chloride intake may be mediated by alterations in systemic calcium homeostasis.¹¹ The fact that there were no significant differences in sodium excretion between normal and hypertensive subjects before calcium infusion reflects similar adherence to prescribed dietary regimens. Hypertensive subjects, however, excreted less potassium than did normal controls, independent of the level of sodium intake. Dietary potassium intake has been reported to be deficient in hypertensive patients,²⁰ and its supplementation may attenuate increases in blood pressure during dietary sodium loading.¹⁹ Because dietary potassium intake was not rigidly controlled in the present study, the reduced fractional potassium excretion may reflect differences in potassium intake²⁰ or intrinsic defects in renal potassium handling. Any alteration in potassium balance in hypertensive subjects may have contributed to the observed differences in blood pressure response to infused calcium.

Systolic and diastolic pressure increased in both normotensive and hypertensive subjects in response to infused calcium under certain dietary conditions. Short-term calcium infusion increases blood pressure primarily because it increases systemic vascular resistance^{21, 22} in both normotensive and hypertensive subjects. Cardiac output may increase during the first several minutes of calcium infusion,²³ but it returns to baseline within 30 minutes of exposure, and the increased pressure is maintained by increased vascular tone.^{21, 22} There is strong evidence that direct vascular effects of calcium play important roles in the increased vascular resistance. Resistance of isolated perfused vascular beds varies directly, in most species, with the calcium concentration of the perfusate near physiological levels.²⁴⁻²⁷ In humans, local calcium infusions, designed to prevent changes in systemic calcium concentration and the resultant changes in circulating hormone levels and central hemodynamics, were shown to increase vascular resistance.²⁸ In rats, however, vasodilation occurs when ambient calcium concentrations are raised.²⁹ Increasing calcium concentrations

near physiological levels in vitro increases vascular tone, while higher concentrations lead to vasorelaxation.³⁰ Together, these studies suggest a role for direct local effects of calcium on vascular smooth muscle in the development of blood pressure changes during calcium infusion.²⁴⁻²⁷

Weidmann and co-workers^{17, 21, 22} have studied possible hormonal consequences of calcium infusion and their contribution to the hemodynamic responses. Calcium infusion significantly increased peripheral levels of norepinephrine but had no effect on renin, aldosterone, or dopamine levels. They suggested that enhanced catecholamine release may participate in the pressor response to infused calcium. Another possible contributor to blood pressure homeostasis during calcium infusion is PTH. Short-term infusion of PTH reduces systemic pressure.^{31, 32} In subjects with secondary hyperparathyroidism, elevated PTH levels may reduce pressure homeostatically, since the increase in systemic pressure during short-term calcium infusion correlates best with the fall in serum PTH.³³ In most studies, the pressor response to infused calcium is not clearly correlated with the increase of serum calcium. This variability of the hemodynamic response suggests that changes in blood pressure during exposure to calcium may be multifactorial in origin and not simply direct effects of calcium itself.

The present results suggest that hypertensive subjects are more sensitive than normal subjects to the acute vascular effects of calcium, at least under certain dietary conditions. Bianchetti et al.²² found no difference in the slope of blood pressure versus serum calcium level during calcium infusion in normal subjects and a small number of hypertensive subjects; however, blood pressure rose in response to a low dose calcium infusion (2 mg/kg/hr) in hypertensive, but not in normotensive, subjects. Vascular reactivity to infused pressors is enhanced nonspecifically in hypertensive subjects, possibly because of structural changes in vessel walls.⁷ Overbeck et al.²⁸ found that local infusions of calcium produced similar increases in vascular resistance in both normal subjects and those with essential hypertension when differences in baseline vascular tone were considered. Since systemic and humoral effects were prevented by infusing calcium locally,²⁸ vascular effects were assumed to be direct. If the direct effects of calcium in normal and hypertensive subjects are similar, then the increased response of hypertensive subjects observed in the present study and suggested by others²² may reflect reduced compensatory mechanisms, altered secondary responses, or differing responses to experimental stress. Weidmann et al.¹⁷ found that subjects with mild chronic renal insufficiency, some of whom were hypertensive, were more sensitive to the hemodynamic effects of calcium than were normal subjects. Mori²³ reported that total peripheral resistance decreased during very short-term calcium infusion in normotensive subjects, whereas resistance did not change in subjects with essential hypertension. Although mean arterial pressure and cardiac index increased in both groups during the infusion described by

Mori,²³ these data suggest that vasodilation early during calcium infusion, either as a compensatory response or as a direct one, is greater in normotensive than in hypertensive subjects. As discussed previously, PTH has been shown to be vasodilative when administered acutely in vivo and in vitro.^{31, 32} If baseline PTH concentrations are higher in hypertensive subjects, then acute suppression of PTH release during calcium infusion might reduce the vasodilative effects of this hormone to a greater extent in hypertensive than in normal subjects.³³

The present results indicate an interaction between sodium intake and the effects of calcium on blood pressure. Diastolic pressure did not increase during calcium infusion when subjects consumed little dietary sodium, whereas it rose during calcium infusion when sodium intake was greater. In normotensive subjects, a rise in systolic pressure was also dependent on dietary sodium intake. When dietary sodium intake was low, systolic pressure actually fell during the calcium infusion. On the other hand, systolic pressure rose in hypertensive subjects when calcium was infused regardless of dietary sodium intake. Thus, hypertensive and normal subjects exhibited frankly different responses to calcium infusion only when dietary sodium was reduced. Under conditions of more typical dietary intake, no qualitative differences were found. These differences suggest disordered interactions between sodium and calcium metabolism in hypertensive subjects.

Increased membrane calcium permeability has been described in tissues from hypertensive animals.⁷ Sodium loading may potentiate the short-term effects of calcium in normal subjects, perhaps by inducing a state of negative calcium balance.¹¹ In hypertensive subjects, however, because of preexisting disorders of calcium and PTH homeostasis,^{12, 34} vascular effects may occur without volume expansion. Rats with spontaneous hypertension exhibit impaired vasodilative responses to infused calcium compared with normotensive controls.²⁹ In human hypertension as well, the balance between vasoconstrictive and vasodilative influences of calcium may be altered.

The effects of acute infusion of calcium on blood pressure, such as those observed in the current study, are quite different from more prolonged exposure to calcium. Dietary calcium loading attenuates the development of hypertension in the spontaneously hypertensive rat as well as its normotensive control, the Wistar-Kyoto rat.^{5, 35} Chronic dietary calcium loading also reduces blood pressure in hypertensive humans.^{9, 34} Chronic elevations of ambient calcium may act to block slow calcium channels and decrease calcium permeability of vascular smooth muscle membranes.³⁶ In fact, such down-regulation of calcium responsiveness by calcium itself may be consistent with the present results. If hypertensive subjects exhibit chronic relative calcium deficiency, as evidenced by dietary surveys,¹⁵ reduced serum calcium levels,^{3, 4} and elevated urinary cAMP excretion,^{1, 2} then a sudden increase in serum level consequent to calcium infusion might stimulate greater vasoconstriction. According to such

a scheme dietary calcium loading should blunt the effects of infused calcium on blood pressure in this group of subjects.

In summary, we have shown that abnormalities of calcium and PTH homeostasis are present in subjects with essential hypertension even when carefully matched with a control population and studied while ingesting similar diets. These abnormalities include evidence of parathyroid gland stimulation and a trend toward increased urinary calcium excretion. We have also shown that calcium infusion causes a greater rise in blood pressure in subjects with essential hypertension than in normal subjects when dietary sodium intake is low. These findings are compatible with the presence of a state of relative calcium deficiency in subjects with essential hypertension, a state that may contribute to the enhanced calcium sensitivity demonstrated in the present study.

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