Role of haemodynamics, catecholamines and renin in acute hypercalcaemic hypertension in man

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Summary
1. The effect of acute hypercalcaemia on blood pressure, blood volume, haemodynamic indices, plasma catecholamines, renin and aldosterone levels was investigated in 10 patients.
2. Calcium infusion (15 mg/kg over 3 h) increased (P < 0.05) plasma calcium and adrenaline levels, blood pressure, total peripheral resistance and packed cell volume. Plasma volume was decreased, and heart rate, cardiac output and plasma renin, aldosterone or dopamine levels were not significantly changed. Plasma noradrenaline was increased only minimally after 3 h of calcium infusion.
3. Mean blood pressure before and during calcium infusion correlated with concomitant serum calcium (r = 0.39; P < 0.02) or adrenaline levels (r = 0.57; P < 0.01); changes in blood pressure correlated with variations in plasma adrenaline (r = 0.68; P < 0.001).
4. Acute hypercalcaemic hypertension is mediated by an increase in peripheral vascular resistance and may be induced by a direct effect of calcium on blood vessels. The calcium-mediated increase in adrenaline release may play a contributory, and plasma volume contraction an inhibitory, role.

Key words: catecholamines, haemodynamics, hypercalcaemia, hypertension, plasma volume, renin.

Introduction
Calcium is an important factor in blood pressure regulation. Acute variations in the blood level of calcium may be accompanied by parallel changes in blood pressure in both experimental animals and man (Maxwell, Elliot & Robertson, 1963; Weidmann, Massry, Coburn, Maxwell, Atleson & Kleeman, 1972; Llach, Weidmann, Reinhart, Maxwell, Coburn & Massry, 1974). Also, chronic states of hypercalcaemia are often associated with hypertension, which in several cases abated after correction of hypercalcaemia (Earll, Kurtzmann & Moser, 1966). The mechanism by which excess calcium induces hypertension is still unclear. Therefore we investigated the role of haemodynamic indices, circulatory volume and plasma renin, aldosterone and catecholamines in the genesis of acute calcium-induced hypertension in man.

Subjects and methods
Ten patients (aged 19–71 years) with normal or mildly elevated blood pressure and serum creatinine ranging from 70 to 247 mmol/l were studied. After placement of catheters into the pulmonary and a brachial artery and a cannula into an antecubital vein, an intravenous infusion of 5% glucose in water was started and maintained at minimal rate (50 ml/h) for 1 h. This infusion was replaced by an infusion of calcium gluconate in 5% glucose solution, delivering 15 mg of calcium/kg over a period of 3 h. Measurements of intra-arterial blood pressure, plasma calcium, renin activity (Sealey, Gerten-Banes & Laragh, 1972), aldosterone (Vetter, Vetter & Siegenthaler, 1973), noradrenaline, adrenaline and dopamine levels (Da Prada & Zürrcher, 1976), and cardiac output (by the Fick principle, in six patients only) were performed at the end of the equilibration period and after 2 and 3 h of infusion; packed cell volume and plasma and blood volumes (by isotope dilution using 131I-labelled human serum albumin) before and after 3 h of infusion of calcium. The methods used are well established in our laboratory.
(Weidmann, De Châtel, Schiffmann, Bachmann, Beretta-Piccoli, Reubi, Ziegler & Vetter, 1977; Weidmann, Beretta-Piccoli, Ziegler, Keusch, Glück & Reubi, 1978). Mean blood pressure (sum of diastolic and pulse pressure) and total peripheral vascular resistance (derived from intra-arterial pressure and cardiac output) were calculated.

Two-tailed Student’s t-test for paired data was used for the statistical comparison of values before and during the experimental procedure. Relationships between the various study parameters were evaluated by linear regression analysis.

**Results**

The results are given in Table 1. Infusion of calcium consistently and significantly increased serum calcium and blood pressure. Moreover, the infusion caused significant increases in total peripheral resistance and packed cell volume. Plasma and blood volumes were decreased significantly (by 9 and 5% respectively), and heart rate and cardiac output remained unchanged. There was a significant progressive increase of plasma adrenaline during the infusion. Plasma noradrenaline was increased only minimally after 3 h of calcium infusion whereas plasma dopamine, renin activity and aldosterone levels were not significantly altered. Individual values of mean blood pressure before and during calcium infusion correlated with corresponding plasma calcium ($r = 0.39; P < 0.02$) and adrenaline levels ($r = 0.57; P < 0.01$); changes in blood pressure correlated with variations in plasma adrenaline ($r = 0.68; P < 0.001$). Calcium infusion was not associated with adverse symptoms; only one patient complained about fatigue 2–3 h after the infusion.

**Discussion**

Acute elevation of serum calcium (+1.1 mmol/l) was associated with a parallel increase in blood pressure, total peripheral vascular resistance and plasma adrenaline levels and with a decrease in plasma and blood volumes. Moreover, blood pressure before and during calcium infusion correlated significantly with concomitant serum calcium levels ($r = 0.39; P < 0.02$). Changes in mean blood pressure during the infusion procedure correlated significantly with the variations in plasma adrenaline levels ($r = 0.68; P < 0.001$).

Calcium can have various effects on the cardiovascular system. It may increase the contractility of both the heart and the peripheral blood vessels (Bohr, 1973; Fabiato & Fabiato, 1979). In this study pulse rate as well as cardiac output were not significantly changed after 2 and 3 h of calcium infusion. Then the hypertensive response was a consequence of an increase in peripheral vascular resistance during acute hypercalcaemia as already reported in one case (Lifschitz, Pak, Henneman, Jawsey, Pilch & Bartter, 1970).

Calcium plays a central role in the excitation–contraction coupling of vascular smooth muscle. It is possible, therefore, that changes in haemodynamics and blood pressure that occur during hypercalcaemia are at least partly due to a direct vascular effect on the cation. Hypercalcaemia may also affect the activity of the sympathetic system or the renin–angiotension–aldosterone axis. The release of catecholamines is calcium-dependent (Rubin, 1970); thus it is possible that

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**Table 1. Effects of intravenous calcium infusion on study parameters**

<table>
<thead>
<tr>
<th>Duration of infusion (h) . . .</th>
<th>0</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca (mmol/l)</td>
<td>2.2 ± 0.1</td>
<td>2.0 ± 0.1***</td>
<td>3.2 ± 0.1***</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>100 ± 5</td>
<td>116 ± 6***</td>
<td>123 ± 7***</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>37.2 ± 2.4</td>
<td>39.4 ± 2.8*</td>
<td>39.4 ± 2.8*</td>
</tr>
<tr>
<td>Plasma volume (ml/kg lean body mass)</td>
<td>54.4 ± 2.5</td>
<td>49.5 ± 2.8***</td>
<td>49.5 ± 2.8***</td>
</tr>
<tr>
<td>Blood volume (ml/kg lean body mass)</td>
<td>86.6 ± 1.8</td>
<td>81.6 ± 2.5*</td>
<td>81.6 ± 2.5*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69 ± 3</td>
<td>65 ± 4</td>
<td>65 ± 3</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.0 ± 0.5</td>
<td>4.8 ± 0.4</td>
<td>4.8 ± 0.5</td>
</tr>
<tr>
<td>Total peripheral resistance (kPa l¹ s)</td>
<td>164 ± 22</td>
<td>206 ± 38*</td>
<td>225 ± 39*</td>
</tr>
<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>0.25 ± 0.04</td>
<td>0.32 ± 0.06*</td>
<td>0.37 ± 0.06**</td>
</tr>
<tr>
<td>Plasma noradrenaline (nmol/l)</td>
<td>1.17 ± 0.25</td>
<td>1.14 ± 0.23</td>
<td>1.36 ± 0.27*</td>
</tr>
<tr>
<td>Plasma dopamine (nmol/l)</td>
<td>0.76 ± 0.08</td>
<td>0.81 ± 0.10</td>
<td>0.80 ± 0.08</td>
</tr>
<tr>
<td>Plasma renin activity (pmol of ANG I h¹ ml¹)</td>
<td>2.02 ± 0.64</td>
<td>1.64 ± 0.52</td>
<td>1.44 ± 0.45</td>
</tr>
<tr>
<td>Plasma aldosterone (nmol/l)</td>
<td>0.17 ± 0.03</td>
<td>0.19 ± 0.05</td>
<td>0.20 ± 0.05</td>
</tr>
</tbody>
</table>
the increased plasma adrenaline concentrations during hypercalcaemia in our patients were due to a direct stimulatory effect of calcium on adrenal medullary discharge. Moreover, the significant correlation between blood pressure and plasma adrenaline levels before and during calcium infusion is consistent with a contributory role of adrenaline in the pathogenesis of hypercalcaemic hypertension. On the other hand, plasma noradrenaline concentrations remained unchanged after 2 h and were increased only slightly by 3 h of calcium infusion, and no noradrenaline–blood pressure interrelationship was found. The increase in blood pressure during calcium infusion was not associated with an increase in plasma dopamine or an activation of the renin–aldosterone axis. The latter finding is consistent with previous findings (Weidmann et al., 1972; Kisch, Dluhy & Williams, 1976).

Circulatory volume, which is yet another important determinant of blood pressure, was decreased after the calcium infusion. The observed reduction in plasma volume (P < 0.001) and increase in packed cell volume (P < 0.05) in our patients is consistent with previous findings (Weidmann et al., 1972; Kisch, Dluhy & Williams, 1976).

In conclusion, these findings demonstrate that acute hypercalcaemic hypertension is mediated by an increase in peripheral vascular resistance. The pressor effect of calcium was not associated with renin–aldosterone activation, or clear-cut biochemical evidence of increased sympathetic nervous activity, and was possibly counteracted, in part, by a decrease in circulatory volume. Hypercalcaemic hypertension may be induced by a direct effect of calcium on blood vessels, and a calcium-mediated increase in adrenaline release may be a contributory factor.

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References


