Chapter V

Discussion

The findings in this investigation indicate that mean arterial blood pressure is affected by an intravenous calcium chloride infusion. An increase in plasma concentration of calcium was significant correlation with mean arterial blood pressure during the experimental period ($Y = 75.096 + 3.338X$; $r = 0.465$; $p<0.01$) (Fig.27). The role of plasma calcium in the regulation of blood pressure has also been reported by several lines of evidence (Erall et al., 1966; Coburn et al., 1969; Rosentall and Roy, 1972; Weidmann et al., 1972; Marone et al., 1980; Bianchetti et al., 1983). Theoretically, intra arterial blood pressure is a function of two cardiovascular parameters; such an effect may be mediated through a primary change in cardiac output or peripheral vascular resistance or both. The present data show that after intravenous calcium chloride infusion, both total peripheral vascular resistance (Fig.5) and renal vascular resistance (Fig.9) increased markedly. Studies the local effect of calcium ions by using local perfusion of the forelimb, kidney or heart in dogs have been shown to cause increases both of arterial smooth muscle contraction and myocardial contractility during a slight elevation of calcium in the perfusate (Frohlich et al.,1962; Haddy et al., 1963). No consistant change in cardiac output has been noted during calcium infusion (Sialer et al., 1967). However, in present study; cardiac output decreased significantly which

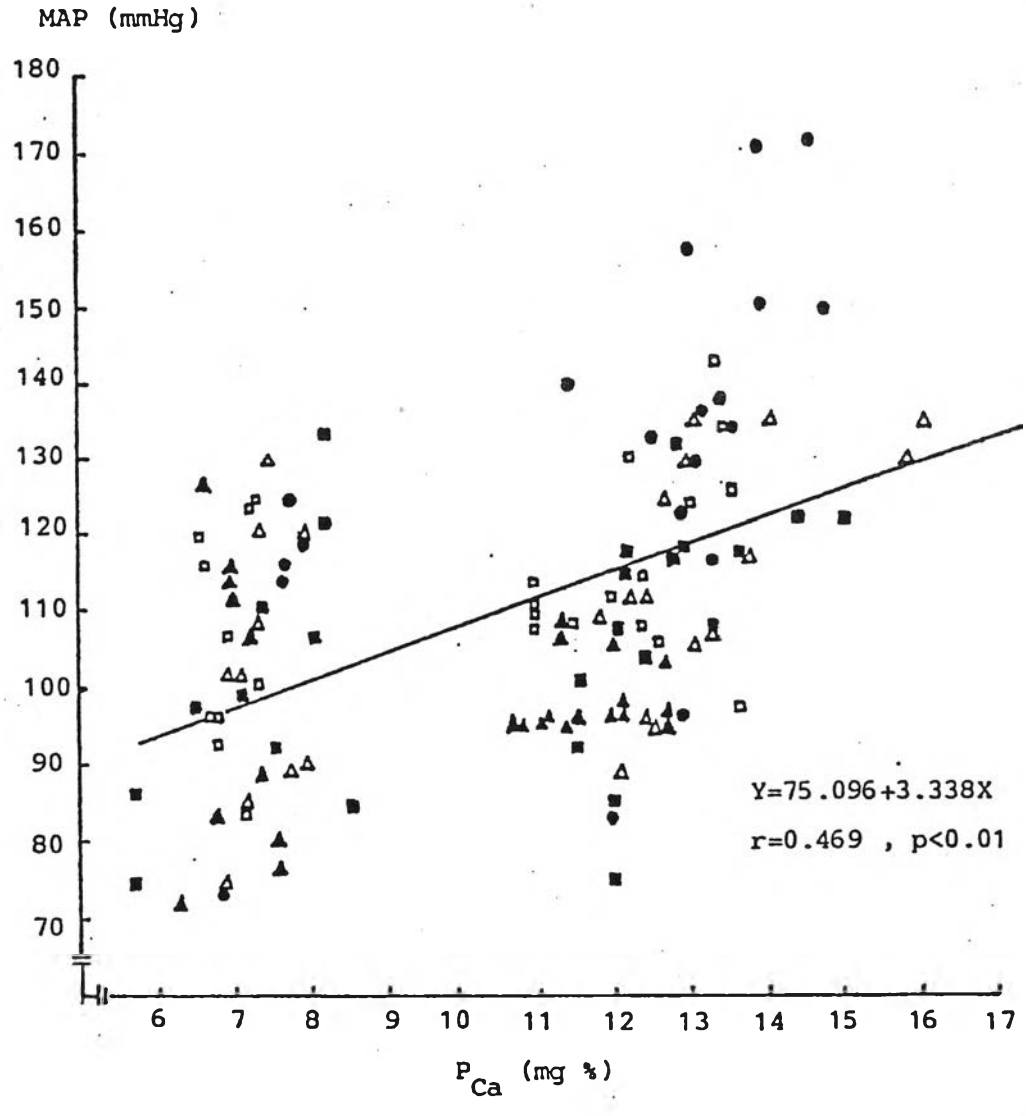

Fig.27: The relationship between plasma calcium concentration (P_{Ca}) and mean arterial blood pressure (MAP) in the dogs group II (●):infused only $CaCl_2$ solution,group III(■):pretreated with low dose of Verapamil,groupIV(△):pretreated with high dose of Verapamil,group V(□):pretreated with Prazosin and group VI (▲):pretreated with high dose of Verapamil and Prazosin

would be resulting from the decrease in stroke volume during elevation of peripheral vascular resistance. It seems likely, therefore, that an increase in peripheral vascular resistance is the major factor underlying the hypertension induced by hypercalcemia.

Calcium ion plays a central role in the coupling between excitation and contraction of striated and vascular smooth muscle cells (Bohr , 1964; Seidel and Bohr, 1971). Contraction process has been known to initiate with a rise of intracellular calcium ions (Ebashi and Ebashi , 1964). The contraction response of isolated smooth muscle has been shown to be progressively higher when calcium concentration was used in the bathing media (Godfraind and Kaba, 1969). It is possible that the cardiovascular changes that occur during hypercalcemia are at least party owing to a direct effect of the cation on the vascular muscle cells (Weidmann et al., 1972). The metabolic pathway by which disturbed calcium homeostasis produces a rise in arterial blood pressure remain unclear. The simplest interpretation of available data suggests that factors that reduce vascular smooth muscle cell exposure to calcium or impair the cell's storage and mobilization of calcium result in increase in peripheral vascular resistance. The vascular smooth muscle cell membrane is less stable, calcium permeability is increased (the slow channels are open), and there is an increase in transmembrane calcium fluxes. As a consequence, smooth muscle tone and contractility are all enchanced (McCarron , 1985).

Animals in group III and group IV which pretreated with calcium channel blocker; Verapamil (inhibition of calcium transport through the voltage-operated channels), could produced the hypotensive action but could not maintain the effect after the combined infusion with calcium chloride solution (Fig.5). Since hypercalcemia may also affect the release of pressor substances such as catecholamines (Marone and Weidmann, 1980). The release of catecholamines is calcium-dependent (Rubin, 1970) and the several experimental data suggest that increased calcium ion activity may augment the release of norepinephrine from sympathetic nerve ending (Burn and Gibson, 1965; Boullin,1967; Kirpeker and Misu, 1967) and epinephrine from adrenal medulla (Douglas and Rubin, 1961). Hypercatecholemia in this setting could induced the vasoconstriction that mediated by with the post synaptic alpha-1 adrenoreceptor (Laher et al., 1986). In the present study, animals in group V ,which pretreated with Prazosin; the selective alpha-1 adrenergic blocker, could produced the hypotensive action but could not maintain the effect after the combined infusion with calcium chloride solution. Under the blockade of both systems (using the combination both of the high dose of Verapamil and Prazosin); in group VI, the mean arterial blood pressure could be in the lower level and maintained the significant hypotensive effect during the period of calcium chloride infusion (Fig.5). Therefore, this observations are consistent with the concept that, in addition to a probably direct effect on cardiovascular contractility, acute hypercalcemia may cause a rise in mean arterial blood pressure by rising cytosolic calcium; and the indirect effect on increase in alpha-1 adrenergic activity. The

present results show that heart rate decreased progressively after intravenous calcium chloride infusion (Fig.2). This phenomenon was also observed by Shiner (1969) that bradycardia occurred when increased plasma calcium level in man. Calcium ion could produce the delay in A-V conductance of heart resulting in prolong Q-T interval and could not generated the normal depolarization of cardiac muscle cells leading to initiate the cardiac arrhythmia (Vander, 1980).

The effects of intravenous calcium chloride infusion on renal hemodynamics and renal functions in the present study (Table 8, 9, 10, 11, 12) demonstrate that calcium ion could produce a marked decrease in renal hemodynamics in group II-V. The significant increase in mean arterial blood pressure following the calcium chloride infusion with a parallel increase in renal vascular resistance (Fig.9) throughout the period of the experiments indicate the local vasoconstriction in the kidney . This effect will cause decrease in effective renal plasma flow, effective renal blood flow and glomerular filtration rate (Fig 6, 7, 8). The increase in renal fraction (group II-VI) after calcium chloride infusion shows that the decrease in cardiac ouput was more than the decrease in effective renal blood flow. An increase in filtration fraction (only in group II-V) after calcium chloride infusion shows that the decrease in glomerular filtration rate was not proportion to the decrease in effective renal plasma flow. But animals in group VI; which recieved of both drugs, filtration fraction was not altered significantly. In the same time periods; effective renal plasma flow effective renal blood flow

and glomerular filtration rate show the slightly increases after the calcium chloride infusion. In the present study, renal vascular resistance in group VI show the significant lower level throughout the experimental periods . Since Verapamil as well as Prazosin act as the vasodilator which could improved the renal hemodynamics (Cavero and Roach, 1980; Godfraind et al., 1986) . It is observed in animals in group VI that mean arterial blood pressure and renal vascular resistance declined in the same pattern while total peripheral vascular resistance did not alter from the control value. These results suggest that kidney plays a major role in the control of blood pressure.

The present data indicate that after calcium chloride infusion, the rate of urine flow increased promptly . These results are similar to experimental and clinical in either acute or chronic hypercalcemia lead to important increase in water and sodium excretion by the kidney (Yofee and Dingman 1960; Eptien , 1968; Suki et al., 1969; Bennett, 1970). These diuretic and natriuretic effects of calcium may be due party to the decrease in proximal fluid reabsorption (Wallach and Carter. 1961; Brian et al., 1974; Vanherweghem et al., 1976; Carol et al.,1977). An inhibitory effect of calcium has also been shown to involve in the hydrosmotic response to vasopressin-dependent adenyl cyclase (Epstein and Whittam. 1966; Nama et al., 1974). During hypercalcemia, sodium and calcium might compete or share on a common reabsorptive site in the nephron (Antoniou et al., 1969) and also decrease sodium reabsorption in the ascending limb of Henle's loop

(Suki et al., 1969; Vanherweghm et al., 1976) resulting an inability to maintain a adequate hypertonicity in the medullary interstitium. Curren and Gill (1962) noted that calcium influenced membrane permeability to sodium by demonstrating that high concentration of calcium in the external medium inhibit transepithelial sodium transport in the frog skin.

In the present study. calcium infusion produced an increase in urinary excretion of potassium this phenomenon has also been shown in the previous studies in dogs (Wolf and Bell, 1949; Wallach and Carter, 1961). The rate of potassium excretion may affected by various factors, primarily by varying the rate of secretion. A rise in the plasma concentration of calcium might stimulate secretion of aldosterone (Issaac et al., 1984) and aldosterone secretion may be increased by plasma volume contraction (Lawrence and Jared, 1982). Aldosterone stimulated secretion of potassium by the distal tubule and collecting duct (Brenner and Rector, 1986). Changes in tubular fluid composition and flow rate have been shown to affect proximal tubular reabsorption of salt and water led to reduce proximal reabsorption of potassium because of the gradient limitation (Lawrence and Jared, 1982). The rate of potassium secretion was also augmented by the increased flow rate. A high flow rate of tubular fluid continually swept secreted potassium away. Therefore, these changes may cause the increase in urinary excretion of potassium although the present study did not measured the aldosterone levels. The reduction of plasma volume and the inhibition of proximal tubular reabsorption of salts and

water as well as the high flow rate of tubular fluid in the present study might be attributed to increase in aldosterone level.

It was observed that plasma concentration of potassium did not decrease while urinary excretion of potassium increased. This phenomenon might be explained by the fact that the alpha and beta adrenergic receptors stimulation by catecholamine, causes potassium release into extracellular fluid (Craig and Mendell, 1957) The increase in excretion of potassium and the increase in shifted potassium from the intracellular compartment might suspect in the proportion ratio which may result to maintain the constant level of plasma concentration of potassium during the experiment.

Hypercalcemia has been shown to produce the changes in the morphological alterations in kidneys (Epstein et al., 1959), localized chieftly to the ascending portion of Henle's loop, distal convoluted tubule and the collecting duct. They consisted of foci hydropic swelling of the tubular epithelial cells, acute necrosis of epithelial and calcification of basement membranes. The necrotic, calcified, cellular debris formed obstructing casts with dilatation proximally. With more prolonged and severe hypercalcemia, the proximal convoluted tubule become involved (Epstein, 1968). And addition, calcium was a potent inhibitor of key enzymes of intermediary metabolism like the "transport" adenosine triphosphatase of cell membrane activated by sodium and potassium (Epstein and Whittam, 1966), phosphofructokinase, pyruvic kinase, pyruvic carboxylase

(Bygrave, 1967). It seems likely that only increase in cytosolic calcium far above the physiological range could significantly impair ATP synthesis (Taylor and Windhager, 1979). A high concentration of calcium with renal cells might be expected to interfere with tubular transport and lead to cellular death (Avioli, 1986) . Therefore, these structural changes were thought to be aparty for the impaired concentrating ability in hypercalcemia. The present results show that during hypercalcemia, animals produced diuresis and natriuresis which resulting in the increase in osmolar clearance and free water clearance. These increases were in the proportion ratio to maintain the constant plasma osmolality levels throughout the experiment.

In present data , the rate of urinary inorganic phosphorus excretion (Fig.26) and plasma concentration of inorganic phosphorus (Fig.16) increase after the administration of calcium chloride solution . It was also observed by Salvesen (1924) in dogs and by Baylor's group (1950) in man. These phenomenons might be explained by the cessation of parathyroid function induced by the hypercalcemia. It seems unlikely that the skelaton, a rich storehouse of phosphorus, would also yeild phosphate in response to hypercalcemia. Since the parathyroid hormone was suppressed, the tubular of inorganic phosphorus elevated markedly (Howard et al, 1953; Howard and Thompson, 1957; Levitt et al., 1958). These results reflect an a rise in a readily filterable substance could result in increase glomerular filtration of this substance an a greater in urinary output (Howard et al., 1953). These results suggest that hypercalcemia produced the

elevation of plasma concentration of inorganic phosphorus caused a shift of cellular phosphorus to the extracellular compartment and increase in renal tubular reabsorption.

In the present results, plasma concentration of sodium and chloride did not alter significantly in spite of its urinary excretion increase. A similar observation was made in anesthetized dogs (Wallach and Carter, 1961) and also described in man and monkey (Levitt et al., 1958). The explaination for these might be that; in vitro (Frakunding and Catt, 1982) and in vivo experiment (Issaac et al., 1984); the level of aldosterone increased following calcium load. Aldosterone caused increase of sodium reabsorption principally at cortical collecting ducts by activated the sodium channels, and coinsidal increase in the transportation of chloride (Brenner and Rector, 1986).

Considering the renin-angiotesin system, it was indicated that an inverse relationship existed between intracellular free calcium concentration and the rate of renin release (Fray et al., 1983). It was noted that no significant change and perphaps a slight decrease in plasma renin activity during acute hypercalcemia (Weidmann et al., 1972; Brinton et al., 1975; Kisch et al., 1976; Marone et al., 1980 ; Park et al., 1981). Regarding the mechanism by which the calcium channel blocker modify plasma renin activity showed that no significant correlation existed between the acute increase in plasma renin and changes in blood pressure induces by Verapamil (Weidmann et al., 1984). The hypercalcemia may well reflect a certain contributory role of

slight sympathetic activation to acute hypercalcemic hypertension (Marone et al., 1980). Catecholamines hyperpolarized the juxtaglomerular cell membrane and cause a net efflux of calcium (Fray et al., 1983). The fall in cytosolic calcium triggered a process which transported renin from the site of synthesis or storage into the cytoplasmic space. It was observed that changes in renin correlated significantly with change in plasma norepinephrine (Weidmann et al, 1984). Therefore, it seems that activity of the renin-angiotensin system plays no relevant pressor role during acute hypercalcemic hypertension but hypercalcemia could modulated renin release by modifying renal perfusion pressure or by increasing tubular sodium delivery to the macula densa (Marone and Weidmann, 1986.).

The plasma volume (Fig.3) markedly decrease during acute hypercalcemia. This phenomenon was also observed in man (Marone et al., 1980). It might be explained that acute hypercalcemia produced a mild fluid loss from the vascular compartment and volume contraction could augmented renal sodium diuresis (Suki et al., 1969). Whatever the exact underlying mechanisms, it is possible that intravascular volume contraction may partly counteract the pressor mechanism of acute hypercalcemia in the animals. These results also produce the parallel declined in blood volume (Fig.3).

In conclusion, these findings suggest that acute hypercalcemic hypertension is mediated by an increase vascular resistance. This hypertension could induced by the direct effect of calcium on the

cardiovascular system (through calcium channels) and by the indirect effect of calcium-mediated increase in catecholamines release (through increasing the activity of alpha -1 adrenoceptors) which may play a contributory role ; and a reduce plasma volume is an inhibitory role. The kidney plays a major role in the control of blood pressure. The intravenous calcium chloride infusion produced the decreases in renal hemodynamics and renal functions as well as the defective in the normal concentration ability of the kidney.