Acute Hypercalcemia-Induced Hypertension: The Roles of Calcium Channel and Alpha-1 Adrenergic Receptor

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Objective : *To study the mechanism (s) of acute hypercalcemia-induced hypertension in dogs.*
Material and Method : *Adult male mongrel dogs were intravenously infused with: 1) normal saline solution, 2) $CaCl_2$ solution, 3) $CaCl_2$ + calcium channel blocker (verapamil), 4) $CaCl_2$ + selective alpha-1 adrenergic receptor blocker (prazosin), or 5) $CaCl_2$ + verapamil + prazosin. Either verapamil or prazosin treatment was started at forty minutes before $CaCl_2$ infusion and then was co-administered throughout the three-hour experimental period. Systemic and renal hemodynamics parameters were determined.*
Results : *Infusion of $CaCl_2$ caused increases in mean arterial blood pressure ($p < 0.01$), total peripheral resistance ($p < 0.001$), and renal vascular resistance ($p < 0.001$). Prior treatment with either verapamil or prazosin lowered baseline blood pressure ($p < 0.01$) and could prevent hypercalcemia-induced hypertension. This occurred accompanying regaining to near normal values of abnormal systemic hemodynamics parameters. Combination of both drugs showed more profound effects, particularly on lowering renal vascular resistance.*
Conclusion : *Acute hypercalemic hypertension is caused by an increase in vascular resistance mediated via the direct effect of calcium on vascular smooth muscle as well as the indirect effect of calcium induced hypercatecholaminemia. The stimulatory effect of hypercalcemia on renal vascular resistance is more prominent than that on peripheral vascular resistance.*

Keywords : *Acute hypercalcemic hypertension, Hypercatecholaminemia, Calcium channel blocker, Alpha-1 adrenergic receptor blocker*

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Calcium is an important factor in the regulation of blood pressure[1]. Acute hypocalcemia could induce hypotension in both experimental animals[2] and humans[3,4]. Conversely, acute[5-15] as well as chronic[16-18] hypercalcemia could cause hypertension. Acute hypercalcemic hypertension appears to be mediated by increased vascular resistance, the mechanisms of which remain unestablished. Hypercalcemia could influence blood pressure by direct action on the vascular muscle cells, or by inducing increments in blood levels of various vasopressive substances[1,7-11,13]. At present, it is believed that the former has the more pathogenetic role in acute hypercalcemic hypertension[1,7,8,12,13,19].

Hypercalcemia and, thus, increased calcium ion influx through calcium channels could have a direct effect on vascular smooth muscle cells[20,21]. Calcium channel blockers could abolish the hypertensive effect of hypercalcemia[10,13,14]. Regarding vasopressive substances, studies related to the activity of renin angiotensin aldosterone system in acute hypercalcemic hypertension have yielded conflicting results[1,7,8,10,12,15]. In contradistinction, hypercatecholaminemia has been demonstrated in hypercalcemia-induced hypertension[7-11]. Indeed, the release of catecholamine is dependent upon calcium

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ion activity[22]. Calcium ion could facilitate the release of epinephrine from the adrenal medulla[21,22] and norepinephrine from sympathetic nerve ending [25,26]. Catecholamines, via binding with alpha-1 adrenergic receptor, could induce vasoconstriction[27]. Heretofore, there are scarce data regarding the abrogatory effect of alpha-1 adrenergic receptor blocker in acute hypercalcemic hypertension. The present study was conducted to determine whether the direct effect of hypercalcemia on vascular smooth muscle cells or the hypercalcemia-induced hypercatecholaminemia is the main underlying mechanism of increased vascular resistance in acute hypercalcemic hypertension. In the present study, the calcium channel blocker and selective alpha-1 adrenergic blocker were used to examine the mechanism(s) responsible for alterations in systemic and renal hemodynamics as well as in blood and urine parameters in acute hypercalcemic hypertension state.

Material and Method

Animals

The experiments were carried out in adult male mongrel dogs, weighing 10-18 kgs. The animals were fasted for 12 hours prior to the study. On the day of the experiment, each dog was anesthetized with intravenous pentobarbital sodium 30 mg/kg BW (Nembutal, S.S.N.A. La Ballasfiere, France). To maintain a state of light anesthesia, supplemental doses of pentobarbital (30-40 mg) were administered, when required, during the study. A tracheal tube was inserted to secure a free airway. Two femoral veins were cannulated with polyethylene tubes (PE 180; Clay Adams, USA), one for infusion of the clearance solution and calcium chloride solution while the other for infusion of the calcium channel blocker (verapamil, Abbott, Germany) or the selective alpha-1 adrenergic blocker (prazosin, Pfizer, Australia). In order to study renal clearance, the priming solution containing 1.2% para-amino hippurate (PAH; Sigma, USA) and 7.5% inulin (Sigma, USA) in isotonic saline solution were administered at the rate of 0.5 ml/kg body weight (BW). Then, the sustaining solution composed of 0.12% PAH and 0.75% inulin were infused at the rate of 2.0 ml/min. The rate of infusion was constantly controlled throughout the experiment by a peristaltic pump (Micro Tube Pump MP-3, Tokyo Rikakikai, Japan). One femoral artery was cannulated with a polyethylene tube (PE 200; Clay Adams, USA) for blood collection and connected to a pressure transducer (Model P23XL, GRASS, USA) for recording of arterial blood pressure (Polygraph, Model 79, GRASS, USA). The left ureter was reached by paracostal incision with a retroperitoneal approach and was tubulated with a polyvinyl catheter (PV 190; Clay Adams, USA) for urine collection.

After one hour of infusion of inulin and PAH solution, and the urine flow rate was stabilized, urine samples were serially obtained with each collection period of 20 minutes. Blood samples were collected at the midpoint of each urine collection. The obtained blood and urine were measured for inulin clearance, PAH clearance, osmolality, and electrolyte concentrations. Packed cell volume of the blood was also determined.

Experimental protocols

As shown in Fig. 1, twenty five dogs were divided into five groups.

Group I (control, n = 5): Normal saline solution (NSS) was intravenously infused at a rate of 1 ml/min via the right femoral vein throughout the experiment.

Group II ($CaCl_2$, n = 5): Each dog was intravenously infused with a $CaCl_2$ solution, 400 mEq/L, with a priming dose of 0.1 mEq/kg BW and continuously followed by 0.01 mEq/kg BW/min. The NSS was continuously infused via the right femoral vein throughout the experiment.

Group III ($CaCl_2$ + verapamil, n = 5): The dogs were treated in the same manner as group II. Forty minutes before infusion of $CaCl_2$ solution, the animals were pretreated with the calcium channel blocker (verapamil), intravenously infused with the priming dose of 0.4 mg/kg BW and followed immediately by verapamil 12 μg/kg BW, at the continuous rate of 1 ml/min. Verapamil was administered in replacing of NSS via the right femoral vein.

Group IV ($CaCl_2$ + prazosin, n = 5): The dogs were treated in the same manner as group III, but the animals were pretreated with the selective alpha-1 adrenergic receptor blocker, prazosin, which was infused intravenously with the priming dose of 1.15 mg/kg BW and followed immediately by the sustaining dose of 20 μg/kg BW at the rate of 1 ml/min throughout the experiment.

Group V ($CaCl_2$ + verapamil + prazosin, n = 5): The dogs were treated in the same manner as group III, but the animals were pretreated with the combination of verapamil and prazosin. The sustaining dose of the combined drugs was infused intravenously at the rate of 1 ml/min throughout the experiment.

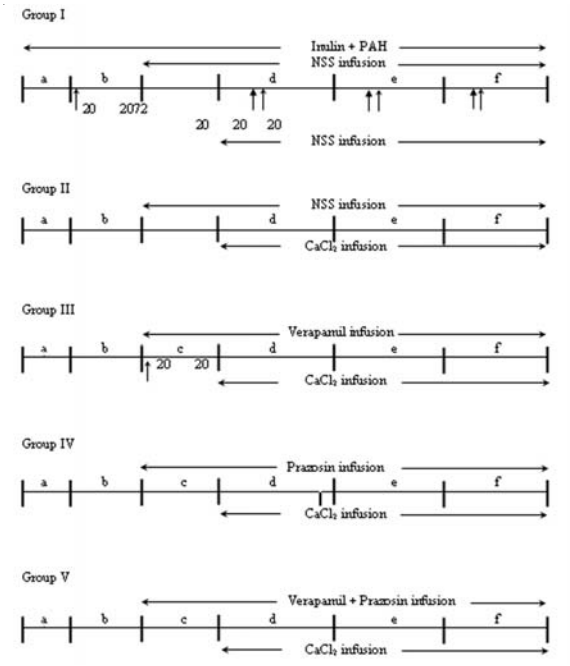

Fig. 1 Diagrammatic illustration of experimental protocols

a = equilibrium period
b = baseline period
c = before $CaCl_2$ infusion period
d, e, f = after $CaCl_2$ infusion period at 1st, 2nd, and 3rd hr
20 = 20 minutes interval of urine collection
= the time that collect series blood samples for cardiac output
= the time that collect blood sample
NSS = normal saline solution

Determination of total peripheral resistance (TPR)

The values of TPR were obtained by the equation

$$TPR = \frac{MAP \bullet 1330 \bullet 60}{CO}$$

Where, MAP = mean arterial pressure
= Pd + 1/3 (Ps-Pd)
(Pd = diastolic pressure, Ps = systolic pressure)
CO = cardiac output

Cardiac output was determined by dye dilution technique using Evans blue (Sigma, USA). This technique has been widely used in several studies in both animals and human[28-30]. The loss of accuracy is minimal[31,32]. In addition, Foldager N and Blomqvist CG[33] performed this technique and compared the results with those from the Pascal Program Computer Analysis. The differences were not statistically significant. In the present study, the CO was measured by using the technique described by Chaiyabutr et al[34]. In brief, a bolus of Evan blue dye solution (0.5%) was injected into the femoral vein. Then, blood samples were serially collected from the femoral artery within 3-5 seconds after the dye injection. Serial samples of arterial blood were obtained via the peristaltic pump. Each sample, approximately 1 ml/sec, was collected for a period of 10-14 seconds. Then, the amount of the dye in each blood sample was measured respectively by spectrophotometry and was calculated as described by Hamilton et al[35].

Determination of renal hemodynamics

Using the Fick's principle, PAH clearance was used for effective renal plasma flow (ERPF) and inulin clearance was used for glomerular filtration rate (GFR). Plasma and urine inulin concentrations (Pin and Uin, respectively) were determined by the antrone method as described by Young and Raisz[36]. Calculation of plasma and urine PAH concentrations (PPAH and UPAH, respectively) were carried out by the method of Marshall as modified by Smith[37].

The following equations were utilized to calculate the values of renal hemodynamics parameters:

$$\text{Glomerular filtration rate (GFR)} = \frac{Uin \bullet V}{Pin}$$
(V = urine volume per 24 hours)

$$\text{Effective renal plasma flow (ERPF)} = \frac{UPAH \bullet V}{PPAH}$$

$$\text{Effective renal blood flow (EBPF)} = \frac{ERPF \bullet 100}{100 - PCV}$$

PCV = packed cell volume, determined by the preperation of blood in an international microcapillary centrifuge (IEC Model MB, Damon, USA) and measured with an international microcapillary reader (IEC 2201, Damon, USA).

$$\text{Filtration fraction (FF)} = \frac{GFR \bullet 100}{ERPF}$$

$$\text{Renal vascular resistance (RVR)} = \frac{MAP \bullet 1333 \bullet 60}{ERBF}$$

Determination of blood and urine parameters

The sodium and potassium concentrations in plasma and urine were assessed by flame photometer (Model 480, Corning, England), chloride by chloride/carbon dioxide analyzer (Model 925, Corning, England), calcium by colorimetric method of

Moorehead and Biggs[38], inorganic phosphorus by the method of Goberi[39], osmolality by freezing point osmometer (Advanced osmometer Model 3D3, USA).

The following formulae were employed to determine the values of urine parameters:

$$\text{Urinary electrolyte excretion} = Ue \bullet V$$

$$\text{Fractional electrolyte excretion (FEe)} = \left[\frac{Ue \bullet V/Pe}{GFR}\right] \bullet 100\%$$

$$\text{Osmolal clearance (COsm)} = \frac{UOsm \bullet V}{Posm}$$

Statistical analysis

All data were expressed as Mean $\pm$ S.E. Statistical significance ($p < 0.05$) was assessed by using analysis of variance (ANOVA). Statistical calculation was obtained by using a commercially available statistics software package (SPSS for Windows v. 10.0, SPSS, USA).

Results

Blood and urine parameters; systemic and renal hemodynamics in the control group

Throughout the experiment, animals in the control group, receiving only NSS infusion, showed no significant changes in blood and urine parameters as well as in systemic and renal hemodynamics (Figs. 2-6).

Effects of $CaCl_2$, calcium channel blocker, and alpha-1 adrenergic receptor blocker on blood parameters

Following $CaCl_2$ infusion, the plasma calcium levels of animals in group II-V were increased from the baseline values, ranging 3.48-3.82 mEq/L to the hypercalcemic levels, ranging 6.18-6.88 mEq/L ($p < 0.001$). No alterations were observed in the plasma levels of sodium, potassium, chloride, and osmolality (data not shown).

Effects of $CaCl_2$, calcium channel blocker, and alpha-1 adrenergic receptor blocker on systemic hemodynamics

In group II, after $CaCl_2$ infusion, there was a sharp increase of mean arterial blood pressure (MAP) from 121 ± 9 to 128.3 ± 12.5 mmHg ($p < 0.05$) within 1 hr, and this was progressively increased and maintained at the higher level till the end of the experiment (Fig. 2). The increased MAP was correlated with the increased plasma calcium levels ($p < 0.001$, data not shown). The total peripheral vascular resistance (TPR) was markedly increased from the baseline values to $273 \pm 22\%$ ($p < 0.01$) and $338 \pm 21\%$ ($p < 0.001$) at the second and third hour period of $CaCl_2$ infusion, respectively (Fig. 3).

Prior to $CaCl_2$ infusion, when animals were treated with verapamil (group III), prazosin (group IV), and the combination of verapamil and prazosin (group V), there were significant decreases in MAP from 116.0 ± 5.0 to 88.3 ± 4.3 ($p < 0.01$), 116.0 ± 5.0 to 95.8 ± 4.0 ($p < 0.01$), and 114.6 ± 3.3 to 80.0 ± 2.8 mmHg ($p < 0.001$), respectively. Verapamil (group III) and prazosin (group IV), could prevent the hypertension, observed in group II, following $CaCl_2$ infusion (Fig. 2). Of interest, animals in group V, which received the combination of verapamil and prazosin, expressed persistently lower

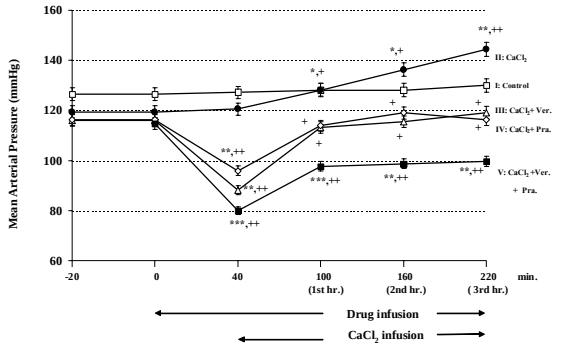

Fig. 2 Mean arterial blood pressure in dogs infused with $CaCl_2$ and pretreated with verapamil (Ver.), prazosin (Pra.), or the combined of verapamil and prazosin (Ver. + Pra.), (n = 5/group, *p < 0.05, **p < 0.01, ***p < 0.001 vs. baseline period of each group; +p < 0.05, ++p < 0.01 vs. time matched control group)

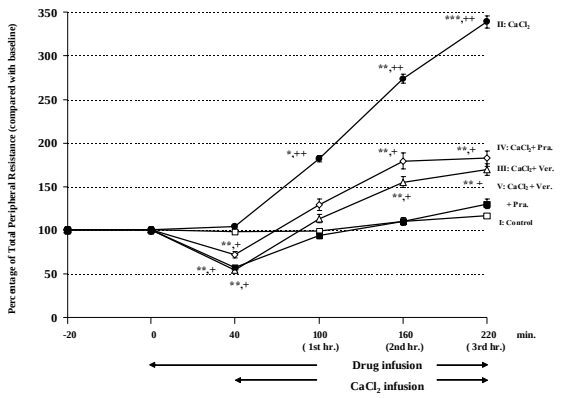

Fig. 3 Total peripheral resistance in dogs infused with $CaCl_2$ and pretreated with verapamil (Ver.), prazosin (Pra.), or the combined of verapamil and prazosin (Ver. + Pra.), (n = 5/group, *p < 0.05, **p < 0.01, ***p < 0.001 vs. baseline period of each group; +p < 0.05, ++p < 0.01 vs. time matched control group)

blood pressure values than the control group throughout the experimental period (Fig. 2). The inhibitory effect of verapamil and prazosin on acute hypercalcemic hypertension was associated with the marked reduction in TPR (Fig. 3). Of note, the values of TPR in group V were not different from the control (Fig. 3). When compared to control, the values of CO were significantly decreased throughout the experimental periods in $CaCl_2$-infused dogs in group II-IV but were not different in group V (data not shown).

Effects of $CaCl_2$, calcium channel blocker, and alpha-1 adrenergic receptor blocker on renal hemodynamics

Infusion of $CaCl_2$ to group II animals caused a significantly progressive increase in renal vascular resistance (RVR, Fig. 4, $p < 0.001$), significantly progressive decreases in effective renal plasma flow (ERPF, Fig. 5, $p < 0.05$), and glomerular filtration rate (GFR, Fig. 6, $p < 0.01$). As seen in figures 4 and 5, pretreatment with either verapamil or prazosin could attenuate the deleterious effects of $CaCl_2$ infusion on renal hemodynamics. When the combination of verapamil and prazosin was co-administered to group V animals prior to $CaCl_2$ infusion, the values of ERPF and GFR returned to the control levels (Figs. 5 and 6). Furthermore, RVR in group V, pretreated with combination of verapamil and prazosin, consistently lowered than those of the control levels (Fig. 4, $p < 0.001$).

Animals in group II which received only $CaCl_2$ infusion had a significantly higher filtration fraction

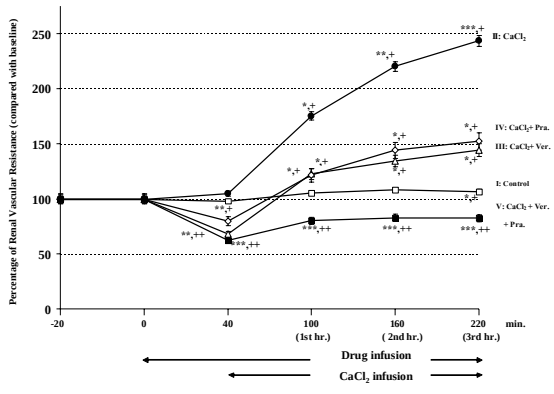

Fig. 4 Renal vascular resistance in dogs infused with $CaCl_2$ and pretreated with verapamil (Ver.), prazosin (Pra.), or the combined of verapamil and prazosin (Ver. + Pra.), (n = 5/group, *p < 0.05, **p < 0.01, ***p < 0.001 vs. baseline period of each group; +p < 0.05, ++p < 0.01 vs. time matched control group)

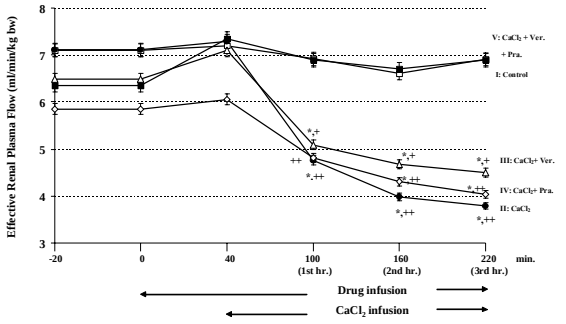

Fig. 5 Effective renal plasma flow in dogs infused with $CaCl_2$ and pretreated with verapamil (Ver.), prazosin (Pra.), or the combined of verapamil and prazosin (Ver. + Pra.), (n = 5/group, *p < 0.05 vs. baseline period of each group; +p < 0.05, ++p < 0.01vs. time matched control group)

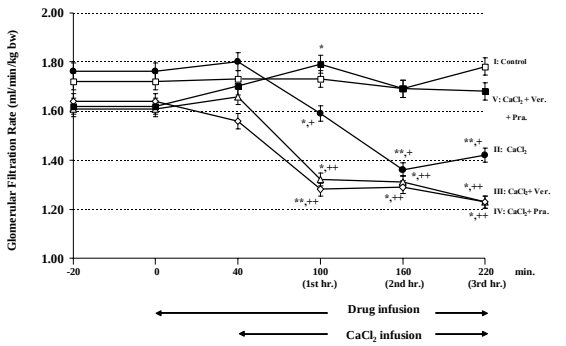

Fig. 6 Glomerular filtration rate in dogs infused with $CaCl_2$ and pretreated with verapamil (Ver.), prazosin (Pra.), or the combined of verapamil and prazosin (Ver. + Pra.), (n = 5/group, *p < 0.05, **p < 0.01 vs. baseline period of each group; +p<0.05, ++p < 0.01 vs. time matched control group)

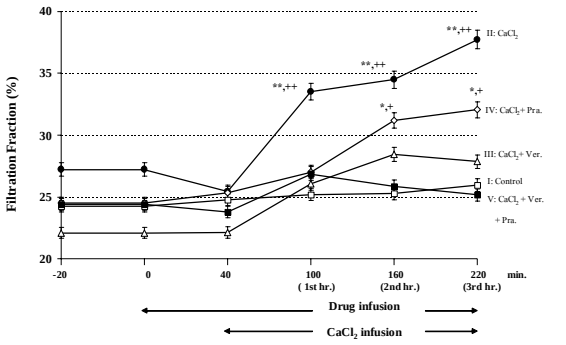

Fig. 7 Filtration fraction in dogs infused with $CaCl_2$ and pretreated with verapamil (Ver.), prazosin (Pra.), or the combined of verapamil and prazosin (Ver. + Pra.), (n = 5/group, *p < 0.05, **p < 0.01 vs. baseline period of each group; +p < 0.05, ++p < 0.01 vs. time matched control group)

(FF) than control (Fig. 7, $p<0.01$). Prior treatment with either verapamil or prazosin could attenuate the increased FF. Of interest, group V animals, pretreated with coadministration of verapamil and prazosin, expressed similar values of FF as the control group (Fig. 7).

Effects of $CaCl_2$, calcium channel blocker, and alpha-1 adrenergic receptor blocker on urine parameters

When compared with the control, all animals in group II-V had a significant decrease in urine osmolality (UOsm) but significant increases in the rate of urine flow (V), urinary osmolal excretion (UOsm • V), osmolal clearance (COsm), and urinary excretion and fractional excretion of sodium, potassium, chloride, calcium, and phosphate (data not shown).

Discussion

The results in the present study have demonstrated that 1) following $CaCl_2$ infusion: a) There were hypercalcemia while plasma levels of sodium, potassium, chloride, and osmolality were unchanged. b) Mean arterial blood pressure (MAP) and total peripheral vascular resistance (TPR) were increased. c) There were significant increases in renal vascular resistance (RVR), and filtration fraction (FF) but significant decreases in effective renal plasma flow (ERPF) and glomerular filtration rate (GFR). 2) Prior treatment with either calcium channel blocker or alpha-1 adrenergic receptor blocker could lower blood pressure from the baseline level and could attenuate the hypertension induced by acute hypercalcemia. The latter occurred in association with conversions of all above abnormal systemic and renal hemodynamic parameters to near normal levels. Combination of calcium channel blocker and alpha-1 adrenergic receptor inhibitor could express more profound effects. 3) Infusion of $CaCl_2$ infusion, alone or incombination with verapamil or/ and alpha-1 adrenergic receptor inhibitor, caused a significant increase in urine flow rate, urinary osmolal excretion, osmolal clearance, and urinary excretion and fractional excretion of sodium, potassium, chloride, calcium, and phosphate.

In the present study, acute hypercalcemia was associated with increased blood pressure. This observation is in agreement with several previous reports regarding acute hypercalcemic hypertension[5-15]. Since blood pressure is the product of cardiac output (CO) and total peripheral vascular resistance (TPR), hypertension would be caused by changes in either one or both factors. The decreased CO but increased TPR observed in the present work would indicate that increased peripheral vascular resistance is the main mechanism of hypercalcemia-induced hypertension. Previous studies regarding the effect of acute hypercalcemia on CO have yielded inconsistent results, most of which show unaltered values[7-9,12,13,40]. The increased peripheral vascular resistance in acute hypercalcemic hypertension noted in the present study concurs with the results of earlier studies[1,5-15,19]. In this regard, elevated calcium in the perfusate locally perfused to forelimb, kidney, and heart in dogs could enhance both arterial smooth muscle contraction and myocardial contractility[41,42]. Acute hypercalemia could increase TPR by direct stimulatory action on vascular smooth muscle cells[1,7,8,12,13,19,21] and, possibly, by enhancing the levels of vasopressive substances[7-11]. Calcium ion plays a central role in the coupling between excitation and contraction of striated as well as vascular smooth muscle cells[1,20,21,43,44]. Contraction process is initiated by a rise in intracellular calcium ion[45].

Either verapamil or prazosin administration could lower blood pressure from the baseline level and could abolish the hypertensive effect of $CaCl_2$ infusion (Fig. 3). The antihypertensive effect of verapamil in acute hypercalcemic hypertension noted in the present study has also been observed in previous studies[10,13,14]. Verapamil would directly inhibit transmembrane transport of calcium through membrane channels[1,7,8,12,19]. Increased levels of catecholamines including epinephrine and norepinephrine have been demonstrated in acute hypercalemic[7-11]. As stated earlier, release of catecholaminemia is positively correlated with calcium ion activity[20-24]. To the authors' knowledge, the present study is the first to demonstrate the effectiveness of alpha-1 adrenergic receptor blocker, prozosin, in acute hypercalcemic hypertension. Prazosin would inhibit the post synaptic alpha-1 adrenergic receptor and, thus, could abrogate the vasoconstrictive effect of hypercalcemia-induced hypercatecholaminemia. When verapamil and prazosin were co-administered, the marked hypotension developed and persisted despite the presence of $CaCl_2$ infusion. Taken together, acute hypercalcemic hypertension is mediated by the direct effect of calcium on vascular contractility and by the indirect effect of calcium via stimulation of catecholamine release and, thus, increased alpha-1 adrenergic activity.

Besides increased TPR, the significantly increased blood pressure following $CaCl_2$ infusion was

also associated with increased renal vascular resistance (RVR), indicating the local vasoconstriction in the kidney. Either verapamil or prazosin alone could attenuate the increased TPR and RVR in animals with acute hypercalcemic hypertension (Figs. 3 and 4). Of interest, $CaCl_2$ -infused animals which were pretreated with the combination of verapamil and prazosin had similar values of TPR but had lower values of RVR than the control values (Figs. 3 and 4). This observation would suggest that renal vasoconstriction plays a more important pathogenic role than systemic vasoconstriction in acute hypercalcemic hypertension. The increased RVR could result in decreases in ERPF and GFR values (Figs. 4 and 5). Following $CaCl_2$ infusion, FF was increased in group II-IV animals, indicating that the decrease in GFR is less than ERPF. Animals in group V, however, had unchanged in FF.

In conclusion, acute $CaCl_2$ infusion could induce hypertension. Acute hypercalemic hypertension is caused by an increase in vascular resistance mediated via the direct effect of calcium on vascular smooth muscle as well as the indirect effect of calcium induced hypercatecholaminemia. The stimulatory effect of hypercalcemia on renal vascular resistance is more prominent than that on peripheral vascular resistance.

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ภาวะแคลเซียมในเลือดสูงอย่างเฉียบพลับทำให้เกิดความดันโลหิตสูง: บทบาทของสารยับยั้งการขนส่งแคลเซียม และสารยับยั้งตัวรับอัลฟาวันอดรีเนอจิค

สมจิตร์ เอี่ยมอ่อง, สมชาย เอี่ยมอ่อง, พงษ์ศักดิ์ พันธุ์สิน, วิศิษฐ์ สิตปรีชา, ณรงค์ศักดิ์ ชัยบุตร

วัตถุประสงค์ *: ทำการศึกษากลไกการเพิ่มขึ้นของความดันโลหิตจากภาวะที่มีแคลเซียมในเลือดสูงอย่างเฉียบพลันในสุนัข*

วัสดุและวิธีการ *: ทำการทดลองในสุนัขพันธุ์มอนเกลที่ได้รับสารทางหลอดเลือดดำดังนี้ 1) น้ำเกลือ 0.9% 2) สารละลายแคลเซียมคลอไรด์ 3) สารละลายแคลเซียมคลอไรด์ และสารยับยั้งการขนส่งแคลเซียม (เวอราพามิล) 4) สารละลายแคลเซียมคลอไรด์ และสารยับยั้งตัวรับอัลฟาวันอดรีเนอจิค (พราโซซิน) หรือ 5) สารละลายแคลเซียมคลอไรด์ เวอราพามิล และพราโซซิน โดยจะเริ่มให้ เวอราพามิล หรือ พราโซซิน ก่อนการให้สารละลายแคลเซียมคลอไรด์เป็นเวลา 40 นาที และทำการให้พร้อมกันทั้งหมดต่อไปอีกเป็นเวลา 3 ชั่วโมง บันทึกค่าการเปลี่ยนแปลงการไหลเวียนเลือดทั่วไปและที่ไต*

ผลการวิจัย *: การให้สารละลายแคลเซียมคลอไรด์ หยดทางหลอดเลือดดำ ทำให้มีการเพิ่มขึ้นของค่าความดันโลหิตเฉลี่ย ($p < 0.01$) ค่าความต้านทานรวมหลอดเลือดแดงส่วนปลาย ($p < 0.001$) และค่าความต้านทานของหลอดเลือดแดงไต ($p < 0.01$) การให้เวอราพามิล หรือ พราโซซิน สามารถลดระดับความดันโลหิตพื้นฐาน และลดระดับความดันโลหิตที่เพิ่มขึ้นจากการให้สารละลายแคลเซียมคลอไรด์ รวมทั้งแก้ไขค่าต่าง ๆ ที่เปลี่ยนแปลงไป ให้กลับสู่ระดับที่ใกล้เคียงปกติ ในขณะที่การให้เวอราพามิล และพราโซซินร่วมกันจะมีผลมากกว่าการให้เพียงตัวเดียว โดยเฉพาะผลต่อการลดลงของความต้านทานของหลอดเลือดแดงไต ที่เกิดขึ้นตลอดการทดลองของการให้สารละลายแคลเซียมคลอไรด์*

สรุป *: การเพิ่มขึ้นของความดันโลหิตจากภาวะที่มีแคลเซียมในเลือดสูงอย่างเฉียบพลัน เป็นผลของแคลเซียมโดยตรงต่อหลอดเลือด และผลของแคลเซียมโดยอ้อมที่เพิ่มระดับแคทีคอลามีนในเลือด ผลดังกล่าวนี้ทำให้กล้ามเนื้อเรียบของหลอดเลือดแดงหดตัว และเพิ่มความต้านทาน ซึ่งหลอดเลือดแดงไตนั้นจะแสดงผลมากกว่าหลอดเลือดแดงส่วนปลาย*