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Cardiovascular Responses to Calcium Administered Intravenously to Man during Halothane Anesthesia

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Calcium chloride (7 mg/kg) was administered intravenously to six healthy volunteers anesthetized with halothane. Cardiovascular changes were measured during constant ventilation and anesthetic depth under three conditions: 1) respiratory alkalosis, 2) normocarbia, and 3) respiratory acidosis. At each Pa_{CO_2}, calcium infusion significantly increased cardiac index, left ventricular minute work index, and stroke index. Heart rate, total peripheral resistance, and cardiac pre-ejection period decreased. No significant change in mean arterial blood pressure or central venous pressure followed calcium administration, and no arrhythmias occurred. It is concluded that calcium administration increases myocardial performance, presumably by increasing the availability of intracellular calcium ion for actomyosin interaction. (Key words: Ions, calcium; Heart, calcium effects; Anesthetics, volatile, halothane.)

SINCE THE CLASSIC STUDIES of Ringer in 1883,[1] many investigations utilizing cardiac muscle or heart–lung preparations have demonstrated the positive inotropic and chronotropic actions of calcium ion on the heart.[2–7] There is some evidence that calcium antagonizes halothane-induced myocardial depression in an isolated system.[8] Studies in the intact animal have yielded conflicting results with regard to the effect of calcium administration on cardiac output.[9,10]

While calcium chloride is commonly used as an inotropic agent in critically ill patients undergoing cardiac surgery, no study has quantitated the magnitude and duration of its cardiovascular effects in anesthetized, normal man. The present study was therefore undertaken in normal man during halothane anesthesia. Since serum concentration of ionized calcium is *p*H-dependent,[11] and since cardiac index is affected by Pa_{CO_2},[12,13] studies were performed under three conditions: 1) respiratory alkalosis, 2) normocarbia, and 3) respiratory acidosis.

Method

Six healthy male volunteers, ranging in age from 21 to 25 years, were selected for study during halothane anesthesia without operation. All subjects received a detailed explanation of the investigational procedures during a preliminary interview. On a return visit they signed a consent form and a complete history and physical examination were obtained. No premedication was given. Anesthesia was induced with halothane in oxygen, and the trachea was intubated without muscle relaxants. A Bird respirator controlled ventilation at constant expired minute ventilation (approximately 150 ml/kg/min) throughout all studies in a given subject. Pa_{CO_2} was controlled by adding CO_2 to the inspired mixture. Halothane was delivered by a Dräger vaporizer into a nonrebreathing system.

Body temperature, monitored by a rectal thermistor probe, was maintained at 36–37 C by infrared heat lamps. Cannulas were inserted percutaneously into the left radial

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TABLE 1. Results of Analysis of Blood before and 16 Minutes after $CaCl_2$ Infusion, Six Subjects

	Serum Ionized Calcium (mM/l)		Total Calcium (mM/l)		Serum Magnesium (mM/l)		Serum Potassium (mM/l)		Serum Sodium (mM/l)	
	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental
Hypocarbia										
Mean	1.04	1.19*	2.63	2.84*	0.712	0.687*	4.34	4.20	137.5	137.7
SE	0.05	0.06	0.07	0.06	0.014	0.010	0.16	0.16	0.4	0.5
Normocarbia										
Mean	1.07	1.19*	2.66	2.84*	0.730	0.715*	4.24	4.25	138.2	138.3
SE	0.04	0.06	0.11	0.10	0.021	0.017	0.26	0.18	0.5	0.4
Hypercarbia										
Mean	1.11	1.25*	2.66	2.81*	0.748	0.732*	4.20	4.37	138.3	138.7
SE	0.03	0.04	0.05	0.05	0.018	0.024	0.15	0.16	0.5	0.5

* Significant difference from control ($P < 0.05$).

artery and into the superior vena cava through the internal jugular vein for blood sampling and measurement of intravascular pressures (Statham strain gauges). The electrocardiogram and electroencephalogram were monitored continuously. Gases from the endotracheal tube were sampled continuously and passed through an infrared analyzer for determination of inspired, end-tidal, and mixed-expired CO_2 concentrations. Inspired and mixed-expired gas samples were analyzed intermittently for halothane concentration by gas chromatography. Expired minute ventilation was measured with a calibrated dry gas meter.

In each subject, the effects of calcium chloride infusion were studied at three levels of Pa_{CO_2}: 1) hypocarbia, 2) normocarbia, and 3) hypercarbia. The sequences of alteration in Pa_{CO_2} were randomized in order to minimize time-related factors influencing cardiac output (*e.g.*, calcium accumulation with repeated doses, and the phenomenon of cardiac output "recovery" with duration of halothane anesthesia).[14] After a new Pa_{CO_2} had been reached, end-tidal CO_2 was maintained constant for at least 15 minutes before measurements were made. Calcium infusions were separated by approximately 30 minutes.

Duplicate control determinations of cardiac output (indocyanine green dye technique) were obtained immediately before injection of calcium chloride (7 mg/kg as a 10 per cent solution) through the central venous catheter over a period of 60 seconds. Cardiac output measurements were then repeated 1, 3, 7, and 15 minutes after calcium infusion. In four subjects, cardiac systolic time intervals were recorded with cardiac output measurements. The electrocardiogram, phonocardiogram, and carotid pulse wave were recorded at 100 mm/sec and analyzed for $Q\text{-}S_2$ (total electromechanical systole), LVET (left ventricular ejection time) and PEP (pre-ejection period). These and other derived values were corrected to zero heart rate using the regression equations described by Weissler.[15]

Under anaerobic conditions, blood samples were drawn for gas analysis and for *p*H, serum ionized calcium, total calcium, magnesium, sodium, and potassium determinations immediately before and 16 minutes after each infusion of calcium chloride. Blood *p*H, P_{CO_2}, and P_{O_2} were determined with a Radiometer electrode system at 37 C. Appropriate corrections were made for the effects of temperature and metabolic changes occurring in blood with the passage of time.[16]

TABLE 2. Cardiovascular Responses

	Cardiac Index (l min m²)		Mean Arterial Blood Pressure (torr)		Central Venous Pressure (torr)		Heart Rate (Beats/Min)		Total Peripheral Resistance (dynes · sec / cm⁵)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Hypocarbia										
Control	2.30	0.21	56.7	2.9	7.5	0.6	64.3	2.9	880	71
1 min	2.56*	0.19	58.6*	3.0	7.4	0.5	60.0*	2.8	807*	53
3 min	2.50*	0.19	57.2	3.2	7.6	0.6	58.0*	3.6	801*	53
7 min	2.51*	0.18	57.6	3.1	7.7	0.6	60.3*	3.2	800	45
15 min	2.51*	0.22	59.2	3.4	7.7	0.6	60.0*	2.7	839	51
Normocarbia										
Control	2.50	0.18	59.3	2.0	7.2	0.8	68.0	2.9	852	77
1 min	2.79*	0.19	63.5	2.8	7.0	0.6	61.7*	3.5	823	60
3 min	2.78*	0.16	60.4	1.6	7.2	0.7	64.3*	3.6	776	55
7 min	2.84	0.12	60.3	1.7	7.1	0.6	63.3*	3.8	748	32
15 min	2.73*	0.16	61.5*	2.3	7.3	0.6	65.7	3.2	802	53
Hypercarbia										
Control	3.15	0.28	64.3	3.7	7.6	0.8	73.0	3.3	745	71
1 min	3.35*	0.27	65.8	4.6	7.8*	0.8	68.6*	3.1	714	67
3 min	3.33*	0.29	63.3	3.5	7.7	0.8	69.7*	3.7	688*	59
7 min	3.39*	0.33	63.3	3.6	7.8	0.8	72.0	3.6	698*	73
15 min	3.30*	0.29	64.5	3.6	7.6	0.8	72.7	3.5	713	67

* Significant difference from control ($P < 0.05$).
† N = 4.
‡ LVET = left ventricular ejection time.

Serum ionized calcium was analyzed with an Orion Research, Inc., flow-through electrode system (Model 88-20) and a Model 801 digital *p*H/mv meter. Blood loss due to sampling did not exceed 500 ml and was replaced with 500 ml of 5 per cent plasma protein fraction in 500 ml of physiologic saline solution as samples were drawn.

Statistical procedures included analysis of variance where comparisons were made among three phases and matched-pairs t tests for comparisons of experimental with control data.

Results

Inspired CO_2 was regulated between zero and 6 per cent to produce hypocarbia (mean Pa_{CO_2} 26.1 torr ± 0.6 SE and mean *p*H 7.536 ± 0.014 SE), normocarbia (mean Pa_{CO_2} 41.6 torr ± 2.0 SE and mean *p*H 7.388 ± 0.014 SE), and hypercarbia (mean Pa_{CO_2} 53.0 torr ± 1.8 SE and mean *p*H 7.304 ± 0.012 SE). Among the three experimental conditions, there were no significant differences in Pa_{O_2}, base excess, minute ventilation, mean airway pressure, body temperature, inspired and mixed-expired halothane concentration, or anesthetic duration. During normocarbia, mean inspired halothane concentration was 1.25 per cent ± 0.13 SE and mixed-expired halothane concentration was 1.04 per cent ± 0.11 SE.

Table 1 lists ion concentrations before and after infusion of calcium chloride. There was a significant correlation between the blood *p*H at the first CO_2 level studied in each subject and the initial control serum ionized calcium measurement: Ca^{++} (mM/l) = 6.84 − 0.785 *p*H; r = 0.763. A similar relationship

to $CaCl_2$ Infusion, Six Subjects

LV Minute Work Index ($\frac{kg \cdot m}{min \cdot m^2}$)		Stroke Index (ml/m^2)		Pre-ejection Period‡ (PEP) (msec)		PEP† / LVET		$\frac{1}{(PEP)^2}$ † ($\frac{1}{sec^2}$)	
Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
1.76	0.19	35.6	2.3	145.1	18.4	0.338	0.050	54.3	12.2
2.04*	0.21	42.8*	2.4	119.5*	15.7	0.282*	0.043	82.5*	21.0
1.94*	0.20	43.0*	1.4	131.2*	10.7	0.307*	0.048	66.9	15.5
1.97*	0.21	41.8*	2.3	133.5	18.7	0.315	0.055	65.7	16.1
2.02*	0.25	41.6*	2.4	139.2	18.6	0.332	0.055	59.9	13.7
2.01	0.18	36.8	2.2	149.8	10.5	0.347	0.032	46.9	7.7
2.40*	0.21	45.4*	2.3	119.6*	9.4	0.278*	0.028	74.4*	13.1
2.27*	0.16	43.4*	2.0	131.7*	10.1	0.306*	0.031	61.5*	11.4
2.31	0.12	45.2*	1.7	136.1	12.3	0.317	0.036	58.7	12.1
2.28*	0.17	41.5*	1.4	140.6	11.2	0.328	0.033	53.6	8.7
2.72	0.24	43.1	2.9	139.6	12.8	0.327	0.035	54.0	7.9
2.96*	0.20	48.6*	2.6	119.2*	10.9	0.282*	0.030	75.5*	12.6
2.84	0.25	47.7*	3.3	129.5*	13.7	0.301*	0.036	65.9	11.6
2.90*	0.28	46.7*	3.0	133.3	13.0	0.313	0.036	60.8	10.3
2.86*	0.24	45.1	2.5	140.6	11.1	0.332	0.028	53.5	8.3

existed between Pa_{CO_2} and the initial control serum ionized calcium in each subject: Ca^{++} (mM/l) = 0.697 + 0.00815 Pa_{CO_2}(torr); r = 0.811. After infusion of calcium chloride (mean dose 587 mg ± 44 SE) there were significant increases in total and ionized serum calcium and significant decreases in serum magnesium at all three CO_2 levels. Control serum ionized calcium increased progressively with each successive dose of calcium chloride in five of six subjects. (Each subject received three injections of calcium chloride, each dose being 7 mg/kg.) None of the alterations in sodium or potassium was statistically significant.

Results of cardiovascular measurements are listed in table 2. Control cardiac index, mean arterial blood pressure, heart rate, left ventricular minute work index, and stroke index increased with increasing Pa_{CO_2}, while control total peripheral resistance decreased with increasing Pa_{CO_2}. At each Pa_{CO_2}, calcium infusion significantly increased cardiac index, left ventricular minute work index, stroke index, and, in the early minutes, $1/(PEP)^2$. There was essentially no change in central venous pressure or mean arterial blood pressure. Heart rate, total peripheral resistance, PEP and PEP/LVET decreased after calcium infusion, although the changes tended to be short-lived. The time courses of some of these hemodynamic changes are illustrated in figure 1. The effects of calcium ion on heart rate and PEP/LVET reached their maximum at one minute and then returned toward control levels. Changes in other variables tended to be more prolonged. Fifteen minutes after calcium infusion, cardiac index and left ventricular minute work index were significantly elevated from con-

trol within each CO_2 level studied. Maximum changes occurred in normocarbic subjects, with the smallest changes in hypercarbic subjects. No arrhythmias occurred after the administration of calcium at any CO_2 level studied.

Discussion

Cardiac index has been reported to increase or to remain unchanged[9,10] following calcium infusion in the intact animal. In a patient undergoing surgical correction of idiopathic hypertrophic subaortic stenosis, Pierce *et al.*[17] found that calcium administration produced a decrease in cardiac output and other hemodynamic changes similar to the changes produced by isoproterenol infusion. In the present study, calcium chloride (7 mg/kg) produced a 10 per cent increase in cardiac index of relatively short duration. Along with the increases in stroke index and left ventricular minute work index, there were decreases in total peripheral resistance and heart rate. These values define the hemodynamic response to calcium injection in normocalcemic, healthy man during halothane anesthesia. This investigation was not designed to test the hypothesis that calcium increases cardiac index by augmenting cardiac contractility; however, the data are consistent with this possibility. It has also been suggested that calcium may play an important role in the regulation of peripheral vasomotor tone.[18,19] Although the effect of calcium on peripheral resistance has not been established in man, animal data suggest that calcium produces peripheral vasoconstriction.[10] Thus, it seems unlikely that the changes in cardiac index observed in the present study were the result of a primary effect on systemic peripheral resistance.

The reduction in heart rate following administration of calcium in man has been demonstrated.[20] It is thought to result from an increase in vagal tone,[10] which may be mediated by baroceptor reflexes. Whereas calcium produces bradycardia in intact man, calcium increases heart rate in the denervated heart.[2,3]

Hemodynamic alterations were smaller after calcium infusion during hypercarbia than after calcium infusion during normocarbia or hypocarbia. Since hypercarbia is known to stimulate endogenous catecholamine release,[21] resulting in increased cardiac output, arterial blood pressure, and heart rate, one might expect that the effect of an inotrope would be reduced under these conditions. Although respiratory alkalosis does reduce serum ionized calcium concentration by increasing the fraction of calcium bound to serum proteins,[11] the magnitude of this effect was small and probably of no hemodynamic significance.

Although the mechanism of halothane-induced depression of myocardial contractility remains obscure, alteration in the availability of intracellular calcium ion for actomyosin interaction may be an important factor. The depression of isometric contractile force caused by halothane in a myocardial muscle preparation is exaggerated when the bathing medium is calcium-deficient.‡ In the dog heart–lung preparation during administration of halothane, the maximal positive inotropic effect of calcium has been reported to be comparable to that of maximally effective doses of norepinephrine.[8] Following the administration of calcium to unanesthetized human volunteers, Shiner *et al.*[20] reported consistently shortened systolic time intervals similar to the results of the present study. Although their method of calcium administration was different (15 ml of 10 per cent calcium gluconate infused over 6 minutes), the magnitude of PEP shortening was less than 10 per cent of control in each subject studied. Cardiac index and Pa_{CO_2} were not reported. The larger changes in PEP (mean maximal decrease = 20 per cent of control value), as well as the significant changes in PEP/LVET and $1/(PEP)^2$, reported in the present study may represent antagonism of halothane-induced cardiac depression by calcium.

‡ Malsch E, Vongvises P, Price HL: Interaction of Ca^{++} and halothane in normal myocardium. Abstract, 1971 Annual A.S.A. Proceedings, pp 111–112.

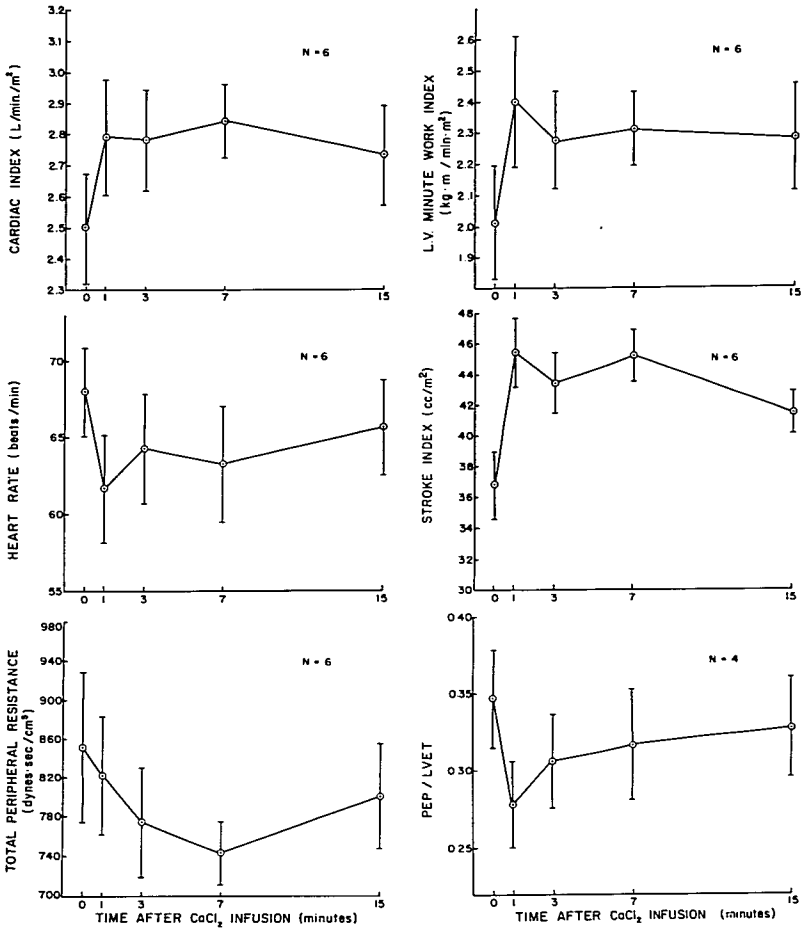

FIG. 1. Time course of cardiovascular changes after intravenous infusion of calcium chloride (7 mg/kg) in normocarbic subjects.

Although PEP correlates inversely with myocardial performance, PEP and LVET are also influenced by changes in heart rate, afterload, and preload.[15,22] Thus, the validity of utilizing PEP or PEP/LVET as an index of myocardial performance when heart rate, afterload and preload are changing simultaneously may be questioned. Since both PEP and LVET have inverse linear relationships to heart rate, individual values are corrected to a common reference point (*e.g.*, zero heart rate) to permit meaningful data analysis. A decrease in afterload produces a decrease in PEP and an increase in LVET.[23] However, these changes are smaller than the decreases in PEP and LVET that accompany an increase in myocardial performance.[15] The marked changes in systolic time intervals in the present study are most consistent with a positive inotropic effect, although a peripheral action of calcium cannot be excluded.

The clinical indications for intraoperative administration of calcium have not been established, and calcium administration is not without risk.[24] Calcium may cause sinus bradycardia, A-V block, increased ventricular irritability, and ventricular fibrillation,[25] particularly in the digitalized patient.[26] Certainly, if profound hypocalcemia can be demonstrated, calcium replacement is recommended. However, facilities for measurement of serum ionized calcium are not generally available, and meticulous use of the flow-through electrode system requires some time for proper anaerobic sample handling and electrode calibration. Until an on-line calcium monitor becomes available, we must rely on clinical judgement to determine those circumstances in which significant hypocalcemia is likely to occur. Examples are operative procedures such as liver homotransplantation and possibly portocaval anastomosis, which present the combined hazards of impaired hepatic function and rapid transfusion of citrated whole blood.[27] Pediatric patients receiving large amounts of citrated whole blood during cardiac surgery may represent another such circumstance.[28] Calcium infusion may be necessary to correct the hypocalcemia following parathyroidectomy. It may also be a useful adjunct to therapy in rare cases of life-threatening hyperkalemia refractory to more routine therapeutic measures.

In absence of factors predisposing to hypocalcemia, routine administration of calcium accompanying citrated whole blood replacement may not be wise because the small and short-lived effects may be outweighed by the attendant risk of cardiac arrhythmias. In selected cases, a therapeutic trial of calcium infusion (*e.g.*, calcium chloride, 3 mg/kg, given slowly intravenously) may be of value. An objective demonstration of improved circulatory function after calcium administration would justify its use.

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Obstetrics

DEATH FROM PCB Two case reports of convulsions and death after administration of 200 to 400 mg lidocaine without epinephrine for paracervical block for abortion are presented. Although no mention of aspiration was made in the first case report, no blood was aspirated before injection in the second. Resuscitation was unsuccessful in both instances. It was recommended that in the future toxic reactions might be avoided by strict adherence to recommended dose and by submucosal injection. *(Berger, G. S., and others: Maternal Deaths Associated with Paracervical Block Anesthesia. Am J Obstet Gynecol 118:1142–1143, 1974.)*