

EFFECTS ON IONIZED CALCIUM OF A CORRECTION OF ACIDOSIS WITH ALKALINIZING AGENTS

A rational basis for the administration of calcium in cardiac resuscitation

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SUMMARY

The effects on the ionized calcium concentration of a correction of various forms of acidosis with sodium bicarbonate or (tris-hydroxymethyl)aminomethane (THAM) were investigated *in vitro* in human plasma. Calculation of least square regression equations of ionized calcium (m mol) on pH yielded the following regression coefficients: hydrochloric acidosis: -0.65 ± 0.06 ; lactic acidosis: -0.27 ± 0.05 ; hydrochloric acidosis corrected with sodium bicarbonate: -0.65 ± 0.02 ; lactic acidosis corrected with sodium bicarbonate: -0.51 ± 0.03 . The results indicate that after correction of lactic acidosis the ionized calcium concentration will be below the control values while pH is restored to the normal range. This effect is even more pronounced when THAM is used. The findings point to the need for calcium administration in cardiac resuscitation.

The recent development of a calcium-selective potentiometric method for the determination of the biologically active form of calcium in plasma—ionized calcium (Moore, 1970)—has led to a re-examination of the effects of pH on this calcium fraction by various investigators. It appears that the increase in ionized calcium associated with a decrease in pH is not independent of the cause of the acidosis. A shift in pH from 7.4 to 6.9 units increases ionized calcium by 0.23–0.40 m mol in hypercapnic acidosis (Hinkle and Cooperman, 1971; Höffken et al., 1971; Pedersen, 1971; Schaer and Bachmann, 1974), whereas an identical pH shift in lactic acidosis increases ionized calcium by only 0.14 m mol (Schaer and Bachmann, 1974). This difference in ionized calcium is explained fully by the formation of calcium lactate complexes (Verbeek and Thun, 1965; Schaer and Bachmann, 1974). It has been suggested that this differential behaviour of ionized calcium in respiratory and lactic acidosis contributes to the differences in the cardiovascular effect of these two forms of acidosis in intact animals or humans (Ligou and Nahas, 1960; Carson et al., 1965; Schaer and Bachmann, 1974).

Correction of lactic acidosis with alkalinizing substances does not eliminate the complex-forming

lactate ions, so that it is to be expected that, after correction, ionized calcium will be less than in controls of the same pH. After a severe metabolic acidosis which is frequently associated with hypoxia, the heart is in a precarious condition, and a decrease in the concentration of ionized calcium may contribute to a fatal outcome. To test the hypothesis that the correction of lactic acidosis results in decreased values of ionized calcium, an experiment was designed to measure ionized calcium during various forms of acidosis and subsequent correction with alkalinizing agents *in vitro*.

METHODS

Human blood was obtained by centrifugation of heparinized blood (4 units heparin/ml) from healthy humans. Aliquots of plasma from the same person were used to perform one complete series of experiments. For every experiment, 2 ml of plasma was equilibrated with a mixture of 5% carbon dioxide in 95% oxygen at 37 °C. For induction of metabolic acidosis, 0.05 ml of a molar solution of hydrochloric or lactic acid was added. Alkalinization was obtained by the stepwise addition of 0.01-ml increments of a molar solution of sodium bicarbonate or THAM ((tris-hydroxymethyl)aminomethane). The total dilution of the plasma sample by the addition of acidifying and alkalinizing solutions did not exceed 5%. Control experiments indicated that this dilution alone did not alter the concentration of ionized calcium significantly.

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Calcium and pH determinations

The pH of plasma was measured with a capillary pH-electrode (Methrom BM 1-108, pH-meter E 388). Ionized calcium was determined with a potentiometric method (calcium-selective flow-through-electrode No 99-20, pH meter model 801, Orion Research Corp., Cambridge, Mass.)* (Moore, 1970). For the calibration of the electrode, standards with their corrected value for the actual concentration of ionized calcium were used, as described previously (Schwartz, McConville and Christopherson, 1971; Schaer, 1974a). Heparin forms a complex with calcium to some extent, so that there is less ionized calcium in heparinized blood than in the corresponding serum (Moore, 1970; Ladenson and Bowers, 1973). In a previous study, however, it has been demonstrated that this effect is negligible, as long as the concentration of heparin does not exceed 10 units/ml (Schaer and Bachmann, 1974). Another problem which had to be considered in this study was the notorious unreliability of calcium electrodes in the presence of high concentrations of hydrogen ions. It has been demonstrated, however, that with the particular electrode employed, the calcium reading was independent of the hydrogen ion concentration as long as the pH was greater than 6.5 units (Ross, 1967; Schaer, 1974a).

Least-square regression equations and the analysis of variance were calculated according to Snedecor (1956) on a desk computer (Olivetti Programma, 101).

RESULTS

Part of a typical experiment is presented graphically in figure 1. After equilibration with 5% carbon dioxide in 95% oxygen (P_{CO_2} 34 mm Hg), 0.05 ml of a molar solution of lactic or hydrochloric acid was added to the plasma sample, corresponding to 0.025 m mol added acid per millilitre of plasma. By the addition of 0.01-ml increments of a molar solution of sodium bicarbonate, the pH was increased again to the range of the control value. A smaller increase in ionized calcium was observed when the plasma sample was acidified with lactic acid than with hydrochloric acid. The plot of ionized calcium against pH indicates a linear regression during alkalization with sodium bicarbonate. The regression coefficients of the least-square regression equations calculated from the individual experiments

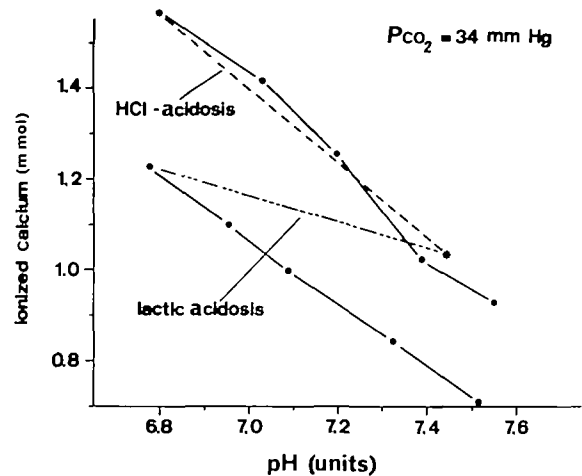


FIG. 1. Part of a typical experiment. The plasma samples, gassed at 37 °C with 5% carbon dioxide in 95% oxygen, pH 7.43 (*), were rendered acidotic by the addition of 0.05 ml of either molar hydrochloric acid or lactic acid. Thereafter, molar sodium bicarbonate was added in increments of 0.01 ml (—). The slopes of the linear regressions of ionized calcium on pH calculated from all the individual experiments are summarized in table I.

are given in table I. This table shows further the statistical evaluation of this factorial experiment in which two types of acidosis (factor one) are alkalized by two different procedures (factor two). The lower part of this table gives the corresponding analysis of variance. Two highly significant results emerge from these calculations. First, the decrease in ionized calcium was greater when the hydrochloric acidosis was treated with alkali. Secondly, correction of either acidosis with THAM lowered the ionized calcium concentration more than did sodium bicarbonate. There was no significant interaction between the alkali therapy and the acidifying agent.

DISCUSSION

It is generally accepted that ionized calcium is regulated within narrow limits under physiological conditions (Moore, 1970; Pedersen, 1972). Alterations in ionized calcium, caused by acute respiratory and metabolic acidosis, however, have persisted *in vivo* for at least 1–2 h, and a close similarity between *in vivo* and *in vitro* experiments has been observed (Hinkle and Cooperman, 1971; Höffken et al., 1971; Schaer and Bachmann, 1974). The *in vitro* experiments reported in this paper extend the previous work and were intended to simulate the behaviour of ionized calcium during acute metabolic acidosis and subsequent correction with an alkalizing agent.

* This instrumentation allows for the determination of ionized calcium with an accuracy of ± 0.01 m mol Ca^{++} , and of pH of ± 0.01 units.

TABLE I. Regression coefficients of the regression of ionized calcium on pH (m mol Ca²⁺/pH unit) during correction of a lactic and hydrochloric acidosis with sodium bicarbonate and THAM (seven experiments for each procedure). Analysis of variance

	Lactic acidosis		Hydrochloric acidosis	
	Sodium bicarbonate	THAM	Sodium bicarbonate	THAM
	-0.4790	-0.6213	-0.6308	-0.8237
	-0.3631	-0.5401	-0.5979	-0.8349
	-0.5484	-0.4425	-0.6474	-0.7655
	-0.6674	-0.7113	-0.6945	-0.8933
	-0.5225	-0.7075	-0.6654	-0.8978
	-0.5348	-0.5425	-0.6389	-0.8133
	-0.4850	-0.5000	-0.7173	-0.7332
Sum	-3.6004	-4.0749	-4.5924	-5.7622
Mean	-0.5143	-0.5821	-0.6560	-0.8232
Acidosis effect	+1	+1	-1	-1
Buffer effect	+1	-1	+1	-1
Interaction	+1	-1	-1	+1

	d.f.	Sum of squares	Mean square	F
Total	27	0.51308		
Treatments	3	0.37020	0.12340	
buffer	1	0.09656	0.09656	16.28
acidosis	1	0.25638	0.25638	48.23
interaction	1	0.01726	0.01726	2.91
Error	24	0.14288	0.00593	

The reason for the dependence of ionized calcium on pH has been attributed mainly to an effect of hydrogen ions on the calcium binding to plasma proteins, but, recently, a further mechanism, a pH-dependent formation of solid calcium carbonate dispersed into particles of colloidal size, has been suggested (Prasad and Flink, 1957; Loken et al., 1960; Peterson, Feigen and Crismon, 1961; Moore, 1970; Pedersen, 1971; Branegard and Oesterberg, 1974).

The slopes of some of the regressions of ionized calcium on the pH are summarized in table II. The values in the upper part of this table are taken from previous experiments in which the acidifying substances have been added in small increments (Schaer and Bachmann, 1974). The data, however, correspond closely with the findings of the present experiments. The great differences between the slopes indicate that a dissociation of calcium from complexes with plasma proteins alone cannot account for all of the effects observed and that other factors have to be considered. The smaller increase in

TABLE II. Summary of slopes of regression of ionized calcium on pH in various forms of acidosis* and during their correction in vitro

Type of acidosis + correction	Slope of regression of ionized calcium on pH (m mol Ca ²⁺ /pH unit)	Change in ionized calcium per 0.5 pH unit
Hypercapnic	-0.57 ± 0.07*	+0.28*
Hydrochloric	-0.65 ± 0.06*	+0.32*
Lactic	-0.27 ± 0.05*	+0.14*
Hydrochloric + Sodium bicarbonate	-0.65 ± 0.02	-0.32
+ THAM	-0.82 ± 0.03	-0.41
Lactic + Sodium bicarbonate	-0.51 ± 0.03	-0.25
+ THAM	-0.58 ± 0.04	-0.28

* According to Schaer and Bachmann (1974).

ionized calcium in lactic acidosis as compared with hypercapnic or hydrochloric acidosis is attributed to the formation of calcium-lactate complexes (Verbeek and Thun, 1965; Schaer and Bachmann, 1974). The data presented confirm the hypothesis that the correction of lactic acidosis with alkalinizing agents will restore the pH to normal while reducing ionized calcium to less than control values. It is noteworthy that the slope of ionized calcium on pH is significantly steeper during the correction of hydrochloric acidosis as compared with lactic acidosis (tables I and II). The reason for this difference cannot be explained. It was observed also that ionized calcium decreased more when the pH was increased by the addition of THAM than when the same effect was obtained with sodium bicarbonate. Binding of Ca²⁺ to THAM might be suspected as the responsible mechanism. This difference between the two alkalinizing compounds, although highly significant, is too small to be of clinical importance.

The metabolic acidosis has been simulated by the addition of 0.025 ml of a molar solution of either hydrochloric or lactic acid per ml plasma, which, according to the terminology of Siggaard-Andersen (1965), corresponds to a negative base excess (-BE) of 25 m mol/litre. This is similar to values occurring during resuscitation after cardiac arrest. The mean changes in ionized calcium likely to occur, together with a lactic acidosis and subsequent correction with sodium bicarbonate or THAM, are shown graphically in figure 2. It can be seen that values of ionized calcium of about 0.15 m mol less than the controls are to be expected when lactic acidosis corresponding to a base excess of -25 m mol/litre is corrected.

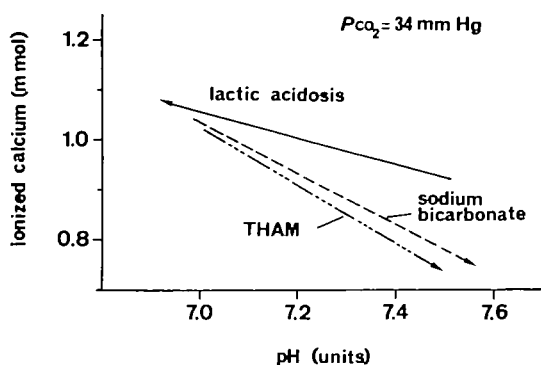


FIG. 2. Graphic representation of the expected changes in ionized calcium when lactic acidosis is corrected with sodium bicarbonate or THAM. Means of seven experiments for each procedure.

The importance of calcium ions for myocardial contraction is recognized generally. It has been demonstrated that the steep part of the calcium-contraction response curve lies in the range of physiological concentrations of ionized calcium, so that even small variations in ionized calcium lead to a considerable effect on contractile force (Winegrad and Shanes, 1962; Seifen, Flacke and Alper, 1964; Schaer, 1974b; Denlinger et al., 1975). In intact animals or humans, the cardiovascular effects of a decreased concentration of ionized calcium have been investigated mainly in connection with the cardiovascular effects of the increased citrate concentration associated with massive blood transfusion.

It has been concluded that a certain decrease in ionized calcium is tolerated well (Krautwald and Dorow, 1939/40; Bunker et al., 1955; Corbascio and Smith, 1967). These experiments, however, have been conducted in healthy animals or humans and the conclusions are predominantly based upon observations of arterial pressure and cardiac output. When more sensitive indices of myocardial contractility are used, a clear negative inotropic effect may be demonstrated following the reduction of the ionized calcium concentration by one-third. This effect was most pronounced when the heart was already depressed by anaesthetic agents or hypoxia and acidosis (Bunker, Bendixen and Murphy, 1962; Corbascio and Smith, 1967; Buckberg et al., 1974).

The administration of alkalinizing agents is accompanied by various secondary effects such as changes in PCO_2 , the sodium concentration, osmolarity and, as described in this paper, ionized calcium. Since the main effect of these compounds (the

correction of the acidosis) will increase the contractile force significantly, a cardiac action of the secondary effects is likely to be obscured by the main effect. However, when care was taken to avoid the secondary effects, a negative inotropic action of both sodium bicarbonate and THAM could be demonstrated (Vaughan Williams, 1955; McElroy, Gerdes and Brown, 1958; Mattiazzi, Cingolani and Gonzalez, 1972). Even when pH changes were allowed to occur, infusion of sodium bicarbonate often resulted in a transient decrease in contractile force. This negative inotropic effect has been assumed to be related to changes in the intracellular hydrogen ion concentration (Vaughan Williams, 1955; Clancy et al., 1967; Chamberlain, Seed and Barrett, 1973). The observation of a decrease in ionized calcium by bicarbonate in physiological solutions (Schaer, 1974a) and in plasma casts doubt on this explanation.

It is the current practice, (Frey, Hügin and Mayrhofer, 1971; Dripps, Eckenhoff and Vandam, 1972) to administer calcium during cardiac resuscitation. These results suggest that the administration of calcium not only causes a transient increase in ionized calcium, but is mandatory if the heart, already depressed by hypercapnia and hypoxia, is to be protected from the negative inotropic effect of alkalinizing drugs.

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EFFETS D'UNE CORRECTION DE L'ACIDOSE A L'AIDE D'AGENTS ALCALINISANTS SUR LE CALCIUM IONISE

Base rationnelle pour l'administration de calcium dans les reanimations cardiaques

RESUME

Les effets d'une correction des diverses formes d'acidose à l'aide de bicarbonate de soude ou d'aminométhane (tri-hydroxyméthyl) (THAM) sur la concentration de calcium ionisé ont été étudiés *in vitro* sur du plasma humain. Le calcul des équations de régression au moindre carré du calcium ionisé (m/mol) sur le pH a donné les coefficients de régression suivants: acidose chlorhydrique: $-0,65 \pm 0,06$; acidose lactique: $-0,27 \pm 0,05$; acidose chlorhydrique corrigée à l'aide de bicarbonate de soude: $-0,65 \pm 0,02$; acidose lactique corrigée à l'aide de bicarbonate de soude: $-0,51 \pm 0,03$. Les résultats obtenus indiquent qu'après correction de l'acidose lactique, la concentration de calcium ionisé sera inférieure aux valeurs témoins lorsque le pH retourne à sa dose normale. Cet effet est encore plus prononcé lorsqu'on utilise du THAM. Ces découvertes portent à croire qu'il est essentiel d'administrer du calcium dans les réanimations cardiaques.

DIE WIRKUNG DER RICHTIGSTELLUNG DER AZIDOSE MITTELS ALKALISCHER AGENTEN AUF IONISIERTES KALZIUM

Rationale Grundlagen bezüglich der Kalzium-Zufuhr während der Herz wiederbelebung

ZUSAMMENFASSUNG

Die Wirkung der Richtigestellung verschiedener Arten von Azidose, mittels doppelsaurem Natron oder THAM

(tris-hydroxymethyl) aminometan) auf das ionisierte Kalzium Konzentrat wurde *in vitro* im menschlichem Plasma untersucht. Berechnung der untersten MQ-Wert Gleichungen des ionisierten Kalziums auf das pH ergaben die folgenden Zuverlässigkeitskoeffizienten: salzsaure Azidose: $-0,65 \pm 0,06$; milchsäure Azidose: $-0,27 \pm 0,05$; salzsaure Azidose, korrigiert mittels doppelsaurem Natron: $-0,65 \pm 0,02$; milchsäure Azidose korrigiert mittels doppelsaurem Natron: $-0,51 \pm 0,03$. Die Ergebnisse weisen darauf hin, dass sich nach Richtigstellung milchsäurer Azidose das ionisierte Kalziumkonzentrat wieder unterhalb der Kontrollwerte befinden wird, während das pH sich in den Normalbereich begibt. Diese Wirkung ist sogar bei Anwendung von THAM noch stärker. Es ist daraus zu schliessen, dass Kalziumzufuhr bei der Herzwiederbelebungstherapie angezeigt ist.

EFFECTOS DE UNA CORRECCION
DE UNA ACIDOSIS CON AGENTES
ALCALIFICANTES SOBRE EL CALCIO IONIZADO

Una base racional para la administración del calcio en la resucitación cardíaca

SUMARIO

Se estudiaron *in vitro*, en plasma humano, los efectos sobre la concentración de calcio ionizado de una corrección de varias formas de acidosis con bicarbonato de sodio o THAM (tris-hidroximetilo) aminometano. El cálculo de las ecuaciones de regresión de los cuadrados mínimos de la milimola de calcio ionizado sobre el pH arrojaron los siguientes coeficientes de regresión: acidosis hidroc্লórica: $-0,65 \pm 0,06$; acidosis láctica: $-0,27 \pm 0,05$; acidosis láctica corregida con bicarbonato de sodio: $-0,65 \pm 0,02$; acidosis láctica corregida con bicarbonato de sodio: $-0,51 \pm 0,03$. Los resultados indican que después de la corrección de la acidosis láctica la concentración de calcio ionizado estará por debajo de los valores de control mientras que el pH retorna a su nivel normal. Este efecto es más pronunciado incluso cuando se usa THAM. Los descubrimientos apuntan hacia la necesidad de administración del calcio en la resucitación cardíaca.