Plasma ionized calcium during paediatric anaesthesia: effects of pH and succinylcholine

C.B. Kancir MD, P. Hyltoft Petersen MSc,
J. Wandrup MD MSc

Variations of plasma ionized calcium and pH were studied in 16 children anaesthetized with halothane and succinylcholine for minor surgery. During anaesthesia, a close negative correlation was noted between pH and ionized calcium. Intubation was followed by a fall of the ionized calcium concentration. A mean decrease of $0.04 \text{ mmol} \cdot \text{L}^{-1}$ was noted, without pH change. The acute elevation of carbon dioxide following extubation allowed the in vivo effects of pH on ionized calcium to be studied. For each pH unit decrease, a mean rise of $0.60 \text{ mmol} \cdot \text{L}^{-1}$ of ionized calcium was found. During the study, no significant variations of plasma total calcium concentration were observed. The variations in the hydrogen ion concentration and the administration of succinylcholine were accompanied by changes of the free calcium ion concentration, due probably to alterations in calcium binding to proteins, and perhaps to the formation of a calcium complex with anions. Our results emphasize the importance of knowledge of the pH for the interpretation of ionized calcium variations in the presence of acid-base disturbances.

Key words

ANAESTHESIA: paediatric; ANAESTHETICS, VOLATILE: halothane; IONS: calcium.

From the Department of Anesthesiology, Sønderborg Hospital (CBK), Sønderborg, and the Department of Clinical Chemistry, Odense University Hospital, Odense, Denmark.

Address correspondence to: Dr. C.B. Kancir, Department of Anaesthesia, Odense University Hospital, DK-5000 Odense C, Denmark.

During anaesthesia for general and cardiac surgery, many interventions have been shown to alter the plasma ionized calcium concentration.^{1,2} Studies in children have been mainly during open heart surgery.^{3,4} It is well known that pH influences the ionized calcium concentration in the plasma.⁵ *In vitro* studies have shown that calcium binding to albumin is pH dependent,^{6,7} but the few *in vivo* studies in humans have conflicting results.⁸⁻¹⁰ In the present study, the variations of ionized calcium and pH were investigated to clarify the blood calcium homeostasis with pH in anaesthetized children undergoing minor surgery.

Methods

Sixteen patients, aged three to nine years (mean five years), all in good health and undergoing routine ear, nose and throat surgery were studied. The institutional ethics committee approved the study protocol and informed parental consent was obtained for each patient.

The children were premedicated with meperidine ($1 \text{ mg} \cdot \text{kg}^{-1}$) together with atropine ($10 \mu\text{g} \cdot \text{kg}^{-1}$) IM. Anaesthesia was induced with incremental concentrations of halothane to a maximum of 2.5 per cent together with 30 per cent oxygen in nitrous oxide by mask using a Bain® system. Following loss of consciousness, succinylcholine ($1 \text{ mg} \cdot \text{kg}^{-1}$) was given intravenously to permit tracheal intubation. The patients were then manually ventilated until the end of anaesthesia, which was maintained with halothane. The anaesthetic time ranged from 30 to 62 minutes. Minimal intravenous infusions of isotonic glucose or normal saline were administered through a peripheral vein.

Blood samples were drawn with minimal stasis from a 16- or 18-gauge intravenous cannula inserted in an antecubital vein in the arm opposite to the one used for fluids and drugs. Venous blood was drawn during the induction of anaesthesia (Sample 1), after the administration of succinylcholine and tracheal intubation (Sample 2), during anaesthesia (Sample 3), and one minute after extubation (Sample 4). The mean duration between the injection of succinylcholine and the second blood sample was 139 seconds (range 120–180 seconds). The third sample was drawn at a mean of 16 minutes (range 11–32

minutes) after succinylcholine injection. Whole blood was collected anaerobically in calcium heparinized syringes and stored on ice water (0–4°C) until processed within one hour of sampling. From blood samples centrifuged for ten minutes and inspected for haemolysis, the serum was stored in small aliquots at –20°C until analysis.

Venous blood pH and PCO₂ were determined at 37°C with an ABL 2® (Radiometer, Copenhagen). Ionized calcium was measured in whole blood and in duplicate at 37°C with a combined calcium ion selective and pH electrode (Model ICA 1®, Radiometer, Copenhagen) (normal range 1.19–1.29 mmol·L⁻¹).^{11,12} Total serum calcium was measured in duplicate by atomic absorption spectrophotometry (Perkin Elmer 403®) (normal range 2.20–2.70 mmol·L⁻¹), and, in the same sample, albumin was measured by the bromocresol green method (normal range 36–50 g·L⁻¹). The duplicates allowed estimation of analytical variation for whole blood ionized calcium (0.5 per cent), serum total calcium (1.5 per cent), and serum albumin (0.8 per cent). The statistical analysis of the data was done by using a non parametric two-way analysis of variance (Friedman) and by linear regression analysis with linear correlation.

Results

Table I records the variations of whole blood ionized calcium, venous pH and PCO₂, serum total calcium and albumin. Venous pH and PCO₂ varied inversely during the study. There was a close negative correlation ($p < 0.001$) between the changes in pH and PCO₂ ($r = -0.97$).

After intubation (Sample 2), the whole blood ionized calcium decreased with pH. During anaesthesia (Sample 3), it continued to fall, whereas pH rose. At the end of anaesthesia (Sample 4), the ionized calcium level increased and pH fell. During all the study period, a negative correlation ($p < 0.001$) was found between

FIGURE Regression lines showing the relationships between the changes in the whole blood ionized calcium concentration ($\Delta WB Ca^{++}$) with pH (ΔpH) (---, ○) at intubation following succinylcholine and (—, ●) at extubation in children.

ionized calcium and pH ($r = -0.52$). The effects of the changes of pH (ΔpH) on ionized calcium ($\Delta WB-Ca^{++}$) at intubation and at extubation are illustrated in the Figure. At intubation (Samples 1 and 2), a mean decrease in pH was associated with a fall of the mean ionized calcium concentration in plasma (Table I). There was a negative correlation ($p < 0.005$) between the changes in pH and ionized calcium ($r = -0.69$). The linear regression for these changes is described by the following equation: $\Delta WB-Ca^{++} = -0.614 \Delta pH - 0.041$.

At extubation, an increase in the mean concentration of ionized calcium was observed with a decreasing pH

TABLE I Venous changes of whole blood ionized calcium (WB-Ca⁺⁺), pHv, PvCO₂, serum total calcium (S-total Ca) and serum albumin (S-alb) during anaesthesia (Mean $\pm$ SD)

	Sample 1	Sample 2	Sample 3	Sample 4	Significance*
WB-Ca ⁺⁺ mmol·L ⁻¹	1.30 $\pm$ 0.02	1.27 $\pm$ 0.04	1.24 $\pm$ 0.03	1.29 $\pm$ 0.03	$p < 0.001$
pHv	7.33 $\pm$ 0.03	7.31 $\pm$ 0.05	7.37 $\pm$ 0.05	7.28 $\pm$ 0.04	$p < 0.001$
PvCO ₂ kPa	5.9 $\pm$ 0.7	6.2 $\pm$ 0.9	5.0 $\pm$ 0.9	6.4 $\pm$ 1.0	$p < 0.001$
Serum total Ca mmol·L ⁻¹	2.44 $\pm$ 0.13	2.43 $\pm$ 0.24	2.40 $\pm$ 0.10	2.41 $\pm$ 0.13	$p > 0.05$
Serum albumin g·L ⁻¹	44.1 $\pm$ 1.1	40.6 $\pm$ 2.0	40.3 $\pm$ 2.5	41.5 $\pm$ 3.0	$0 < 0.001$

*Friedman.

Sample 1 = after induction of anaesthesia, Sample 2 = after intubation, Sample 3 = during anaesthesia, Sample 4 = after extubation.

(Table I, Samples 3 and 4). the changes in pH and ionized calcium showed a negative correlation ($p < 0.01$, $r = -0.66$). The linear regression equation was: $\Delta WB-Ca^{++} = -0.580 \Delta pH + 0.004$.

Discussion

During anaesthesia for minor surgery in children, acid base changes, mainly of respiratory origin, were accompanied by changes of the ionized calcium concentration and by insignificant variations of the total calcium level. The overall correlation was an inverse relationship between ionized calcium and pH. The albumin concentration (Table I) was higher at the start (Sample 1) and at the end of the anaesthesia (Sample 4). This was probably due to increased venous stasis during the taking of the blood samples. Stasis is known to increase the concentration of albumin and total calcium without any change of the ionized calcium level.¹³

Following the administration of succinylcholine and intubation, the ionized calcium concentration decreased (Table I), as we reported previously in a study comparing the effects of succinylcholine on serum calcium concentration, using two different induction techniques.¹⁴ The whole blood ionized calcium falls less than the serum ionized calcium measured at pH 7.40 ($0.03 \text{ mmol} \cdot \text{L}^{-1}$ vs $0.04 \text{ mmol} \cdot \text{L}^{-1}$). However, the ionized calcium variations were similar in the two studies when the changes in anaerobic whole blood were corrected for pH variations (Figure).

In adults and older children, some authors have reported a fall in the total calcium concentration, possibly due to the migration of calcium ions within muscle cells during the fasciculations induced by succinylcholine.^{15,16} However, in the present study, the ionized calcium level decreased although the total calcium concentration remained unchanged. Some complex and unknown mechanisms may have influenced the movement of calcium ions, the calcium binding to proteins, and the formation of the calcium complex with anions, such as bicarbonate, phosphate, citrate and lactate.

After extubation, the ionized calcium level increased, whereas the total calcium concentration remained unaltered. The ionized calcium changes were closely related to the pH variations caused by the acute increase in carbon dioxide levels which followed extubation. The acute respiratory acidosis increased the free calcium ion activity in plasma by liberating calcium ions from its albumin binding sites.^{6,7} Some discrepancies appear in the results of the few reports⁸⁻¹⁰ of ionized calcium changes induced by respiratory acid-base variations in humans (Table II). Comparison is difficult because all the studies did not report adequately the albumin, total calcium and bicarbonate concentrations which are known to influence the

TABLE II *In vivo* investigations of ionized calcium during respiratory acidosis in humans

Authors	Methods of ionized calcium determination	Increase in ionized calcium per pH unit decrease*
Hinkle <i>et al.</i> (1971)	Serum (Orion 88-20)	0.34 $\text{mmol} \cdot \text{L}^{-1}$
Drop <i>et al.</i> (1978)	Whole blood (Orion SS-20)	0.49 $\text{mmol} \cdot \text{L}^{-1}$
Thode <i>et al.</i> (1983)	Whole blood (Radiometer ICA 1)	0.54 $\text{mmol} \cdot \text{L}^{-1}$
Kancir <i>et al.</i> (present paper)	Whole blood (Radiometer ICA 1)	0.60 $\text{mmol} \cdot \text{L}^{-1}$

*Values calculated from data given in the different papers.

plasma ionized calcium variations with pH.^{6,17} Moreover, in our study, it cannot be ruled out that the effects of succinylcholine on ionized calcium had worn off at the time of the drawing of the two last blood samples. However, the slopes of the changes in ionized calcium with pH at intubation and at extubation are parallel in our patients (Figure). This may indicate that the results found at extubation may reflect to some extent the *in vivo* ionized calcium changes with pH in children.

In conclusion, this study demonstrated a fall in ionized calcium concentration following succinylcholine administration and intubation during halothane anaesthesia in children. Further, it serves as a reminder of the importance of the acid base status for the interpretation of the ionized calcium changes occurring during anaesthesia.

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Résumé

Les variations de la calcémie ionisée et du pH sanguin ont été étudiées chez 16 enfants au cours d'une anesthésie à l'halothane et à la succinylcholine, pour une intervention chirurgicale mineure. Au cours de l'anesthésie, une corrélation négative fut notée entre le pH et le calcium ionisé. L'intubation trachéale fut suivie d'une baisse de la calcémie ionisée. On a remarqué une diminution moyenne de $0.04 \text{ mmol} \cdot \text{L}^{-1}$, sans qu'il n'y ait de changement dans le pH. L'augmentation aiguë de gaz carbonique à la suite de l'extubation, a permis l'étude in vivo des effets du pH sur la concentration du calcium ionisé. On a trouvé une augmentation moyenne de $0.60 \text{ mmol} \cdot \text{L}^{-1}$ du calcium ionisé pour chaque diminution d'unité de pH. Au cours de l'étude on n'a trouvé aucune variation significative de la calcémie plasmatique totale. Les variations de la concentration de l'ion hydrogène et l'administration de succinylcholine s'accompagnaient de certains changements dans la concentration du calcium ionisé, probablement par suite des changements du calcium se liant aux protéines, et peut-être par suite de la formation d'un complexe entre le calcium et les anions. Nos résultats soulignent l'importance de la connaissance du pH sanguin pour l'interprétation des variations de la calcémie ionisée, en présence de troubles acido-basiques.