

HYPOCALCAEMIA DURING RAPID BLOOD TRANSFUSION IN ANAESTHETIZED MAN

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SUMMARY

In anaesthetized patients, administration of citrated whole blood for 5 min at controlled rates of 50, 100 and 150 ml/70 kg/min resulted in decreases in the calcium ion concentration (Ca^{2+}) of 14, 31 and 41%, respectively. Ca^{2+} returned rapidly to the control values after termination of the transfusion. Reciprocal changes in serum citrate concentrations occurred, suggesting that the transient hypocalcaemia was a result of redistribution of citrate and hepatic or renal clearance from the vascular space. The total serum calcium concentration did not change significantly during rapid blood administration. Normal saline infusion at 100 ml/70 kg/min caused no change in Ca^{2+} ; however, plasma protein administration at this rate resulted in an 18% decrease in Ca^{2+} , presumably as a consequence of the binding of calcium ions to anionic sites on plasma protein. Hypocalcaemia accompanying blood transfusion is a transient phenomenon, dependent on the total dose of citrate administered and the rate of infusion. Rational calcium replacement therapy during massive blood transfusion may now be based on direct Ca^{2+} measurement.

Recent studies have shown that transfusion of citrated whole blood leads to a decrease in serum ionized calcium concentration (Ca^{2+}) which results from chelation of calcium by citrate (Hinkle and Cooperman, 1971; Perkins et al., 1971). In anaesthetized man, Ca^{2+} has been reported as little as 0.5 m mol/litre (Das et al., 1971). Hypocalcaemia of this magnitude may cause marked cardiac depression in experimental animals and man (McLean and Hastings, 1935; Bunker, Bendixen and Murphy, 1962). In the present study we have measured the degree and duration of the hypocalcaemia which accompanies administration of either citrated whole blood or a 5% solution of plasma protein fraction, at constant flow rates. Restoration of normal Ca^{2+} following blood transfusion may be a result of clearance of citrate from the vascular space or mobilization of calcium ions from skeletal stores. To evaluate the

relative importance of these homeostatic mechanisms, the serum total calcium (TCa) and the serum citrate concentration were determined also during rapid blood transfusion.

METHODS

Thirty patients, without hepatic or renal disease and who required radical cancer surgery, and in whom Ca^{2+} was normal, were selected for study. Informed consent was obtained. Following premedication with morphine and hyoscine, anaesthesia was induced with thiopentone and maintained with enflurane, fluorene or halothane in 50% nitrous oxide in oxygen. Suxamethonium was used to facilitate tracheal intubation and ventilation was controlled mechanically to maintain a constant end-tidal carbon dioxide concentration as measured with a Godardt Capnograph. Body temperature, arterial and central venous pressures and e.c.g. were monitored continuously. When surgical blood loss necessitated volume replacement, arterial samples were obtained anaerobically for control measurements of Ca^{2+} and citrate concentration and for arterial blood-gas analysis. Citrated whole blood, 5% plasma protein fraction solution or normal saline was then administered at a constant rate over a 5-min period with a calibrated 1500-ml syringe. Arterial samples for calcium and citrate analysis were then obtained at 1-min intervals during the 5-min infusion period, for 5 min thereafter and at 10 min after completion of the infusion. The serum citrate concentration was determined using standard fluorimetric enzymatic

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analysis (Lowry and Passoneau, 1972). This method permitted use of microlitre quantities of serum, since it is capable of detecting as little as 0.1×10^{-6} m mol/litre of citrate. Ca^{2+} was measured using an Orion Research flow-through calcium electrode, Model 99-20, according to the method outlined by Hattner and others (1970). These investigators have shown this method to be a sensitive and precise system for the anaerobic determination of serum ionized calcium activity. Arterial PO_2 , PCO_2 and pH were measured with appropriate electrodes and standard corrections for time and temperature were applied.

Patients were grouped according to the substance administered and the rate of infusion (table I). Groups I to III received citrated whole blood warmed by passage through a coil maintained at 35–37 °C. Blood transfusion rates, calculated on the basis of body weight, were 50, 100 and 150 ml/70 kg/min. Group IV received normal saline and Group V received 5% plasma protein fraction (Plasmanate—Cutter Laboratories), both infused at a rate of 100 ml/70 kg/min. Serum total calcium, citrate and potassium concentrations were measured in four patients included in Group II; Ca^{2+} measurements were obtained in the remaining 26 patients. Control measurements and changes accompanying i.v. infusion were analysed using Student's *t* test.

RESULTS

Control serum ionized calcium concentrations are summarized in table I, and ranged from 0.94 to

1.17 m mol/litre (mean = 1.07; SEM = 0.01). Control measurements of serum ionized calcium, arterial pH and PaCO_2 did not differ statistically among the five groups. The mean control citrate concentration was 0.074 m mol/litre (SEM = 0.005) and serum total calcium was 2.15 m mol/litre (SEM = 0.04).

Ca^{2+} decreased significantly from the control value ($P < 0.01$) during blood transfusion at each flow rate studied (fig. 1). The maximum decreases from control were 14, 31 and 41% at infusion rates of 50, 100 and 150 ml/70 kg/min, respectively. Ca^{2+} returned rapidly to near normal values after blood transfusion. No significant change in Ca^{2+} occurred in the five patients who received normal saline at

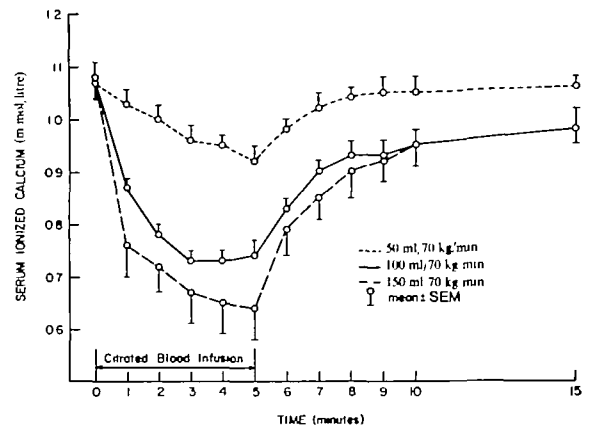


FIG. 1. Ca^{2+} during and following blood transfusion at three controlled flow rates.

TABLE I. Control measurements of Ca^{2+} , pH and Paco_2 in five groups of patients

Group	No. patients	I.v. infusion	Infusion rate (ml/70 kg/min)	Control measurements*		
				Ca^{2+} (m mol/litre)	pH (units)	Paco_2 (mm Hg)
I	5	Citrated whole blood	50	1.07 ± 0.03	7.38 ± 0.02	39 ± 2
II	10	Citrated whole blood	100	1.07 ± 0.04	7.43 ± 0.01	37 ± 1
III	5	Citrated whole blood	150	1.08 ± 0.04	7.42 ± 0.02	43 ± 2
IV	5	Normal saline	100	1.08 ± 0.02	7.39 ± 0.02	42 ± 4
V	5	5% plasma protein fraction	100	1.04 ± 0.01	7.44 ± 0.04	41 ± 3
Total	30			1.07 ± 0.01	7.41 ± 0.01	40.8 ± 1.0

* Mean \pm SEM.

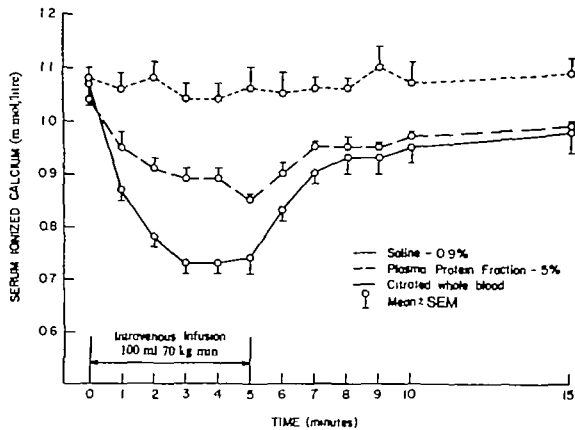


FIG. 2. Ca^{2+} during and following infusion of normal saline, 5% plasma protein fraction and citrated whole blood at a controlled flow rate of 100 ml/70 kg/min.

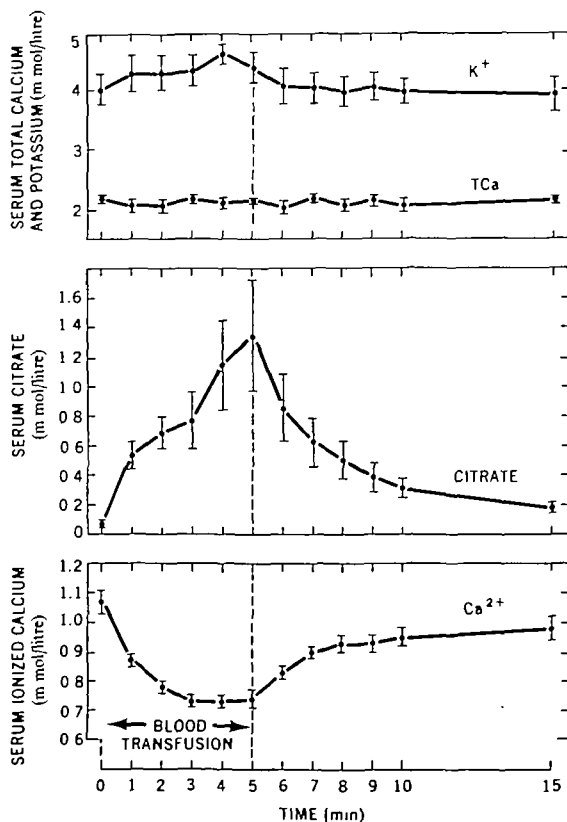


FIG. 3. Calcium, citrate and potassium changes during blood transfusion at 100 ml/70 kg/min in four patients. Points represent mean values; bars represent 2 SEM.

100 ml/70 kg/min (fig. 2). However, administration of 5% plasma protein fraction at this flow rate did produce an 18% decrease in Ca^{2+} . Figure 3 shows that TCa did not change significantly during blood transfusion at 100 ml/70 kg/min. Serum citrate increased from a control value of 0.074 m mol/litre to a peak of 1.35 m mol/litre during infusion of citrated whole blood at 100 ml/70 kg/min. The time course of the decrease in serum citrate following transfusion was similar to that of the increase in serum ionized calcium during this time interval. There was a transient increase in serum potassium near the end of the transfusion.

Serial measurements of arterial blood-gases in four patients who received citrated whole blood at 100 ml/70 kg/min are shown in table II. Noteworthy are the slight increase in PCO_2 and slight decrease in pH, both of which returned to normal 10 min after completion of transfusion.

TABLE II. Arterial PO_2 , PCO_2 and pH in four patients who received citrated blood at 100 ml/70 kg/min

	PO_2^* (mm Hg)	PCO_2^* (mm Hg)	pH* (units)
Control	147 ± 10	33 ± 1	7.43 ± 0.02
End of transfusion	149 ± 10	36 ± 1	7.38 ± 0.11
5 min after transfusion	154 ± 6	34 ± 2	7.43 ± 0.01
10 min after transfusion	157 ± 11	33 ± 2	7.42 ± 0.02

* Mean ± SEM.

The average mean arterial pressure was 85 mm Hg (SEM = 6) at the start of blood transfusion; mean arterial pressure increased less than 10 mm Hg during rapid blood transfusion in all patients. Increases in central venous pressure ranged from 2 to 8 mm Hg. No arrhythmias occurred during any of the study intervals. Body temperature ranged from 35.5 to 37 °C.

DISCUSSION

Total serum calcium is composed of three fractions: ionized calcium (Ca^{2+}), protein-bound calcium (CaProt) and diffusible calcium complexes (CaR). These fractions are in a state of dynamic equilibrium (fig. 4). Ionized calcium, which comprises approximately 47% of the total calcium in normal man, is the physiologically active moiety (Moore, 1970). Recent advances in electrode technology have made it possible to measure calcium ion activity directly, and normal values in awake man have been reported

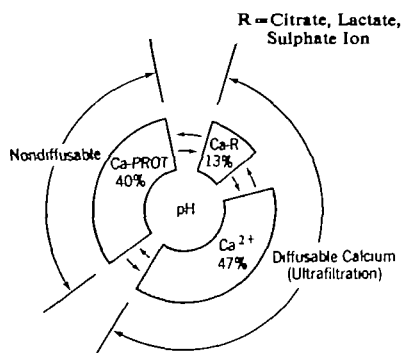


FIG. 4. Distribution of bound and ionized calcium in serum.

to range from 0.95 to 1.25 mmol/litre (Moore, 1970; Hansen and Theodorsen, 1971; Pittinger, Chang and Faulkner, 1971; Ladenson and Bowers, 1973). Thus our control measurements of Ca^{2+} in anaesthetized man are in close agreement with those reported in awake man.

Although factors such as temperature, serum pH and protein concentration are known to affect Ca^{2+} , the calcium changes which we observed during rapid blood transfusion are principally a result of citrate-binding. The effect of decreased temperature is to decrease the binding of calcium to protein; however, temperature-induced pH changes tend to increase protein binding at lower temperatures. These opposing factors are of similar magnitude, and the net effect of lowering temperature from 37 °C to 24 °C is to increase Ca^{2+} by approximately 2% (Hansen and Theodorsen, 1971). The magnitude of pH-induced changes in protein-binding of calcium is also small in the physiological range; a change in pH of 0.1 unit results in a 5% change in calcium ion activity (Hinkle and Cooperman, 1971). The decrease in mean arterial pH from 7.42 to 7.38 during blood transfusion at 100 ml/70 kg/min observed in the present study would tend to decrease protein-binding of calcium, causing a small increase in Ca^{2+} . Finally, the calcium changes which we observed cannot be attributed to a dilutional effect, since acute haemodilution by rapid infusion of normal saline produced no significant change in Ca^{2+} .

The magnitude of hypocalcaemia and the excess of citrate observed in the present study are similar to that reported by Bunker and others (1955) in patients receiving multiple transfusions of citrated whole blood at slower transfusion rates. It is apparent that both the total quantity of citrate administered and the rate of injection are important factors in deter-

mining the magnitude of hypocalcaemia. Killen and colleagues (1971) did not observe hypocalcaemia in three of four experimental animals given ACD solution 2 ml/kg i.v. over a 1-min period. However, they measured Ca^{2+} 5 min after this large dose of citrate. It is likely that more frequent measurements would have revealed marked but transient hypocalcaemia.

The rapid increase in Ca^{2+} following blood transfusion, which we observed, is similar to that observed following exchange transfusion in experimental animals and in man (Perkins et al., 1971; Friedman, Hanley and Radde, 1972; Maisels et al., 1974). Return of Ca^{2+} to near normal values 10 min after multiple-unit blood transfusion has also been reported in anaesthetized man (Hinkle and Cooperman, 1971). The mechanism of acute calcium rebound may be explained on the basis of rapid mobilization of calcium ions from skeletal stores, renal and hepatic clearance of citrate, or simple redistribution of exogenous citrate in extracellular fluid. Although hormonal mechanisms are undoubtedly important in the long-term maintenance of normocalcaemia, parathormone-induced Ca^{2+} changes are too slow to account for the rapid changes which we observed (Parsons, Neer and Potts, 1971). Indeed, if normocalcaemia were restored by a net influx of calcium ions into the vascular space, TCa should increase as Ca^{2+} increases. Since this did not occur in the present study, it is doubtful that skeletal mobilization of calcium is responsible for the acute calcium rebound. However, there was a similarity between the time course of Ca^{2+} and citrate changes, suggesting that an increase in Ca^{2+} is a result of redistribution of citrate in extracellular fluid or citrate clearance by the liver and kidney, or both.

The isolated liver is capable of removing nearly 100 times the normal concentration of plasma citrate from a perfusate with a large citrate concentration in a single passage (Howland et al., 1955). Renal citrate excretion has been measured in dogs with increased citrate concentrations in the blood (Gomori and Gulyas, 1944), and there is some evidence that the kidneys may be important in restoring normocalcaemia after exchange transfusion. Whereas TCa remained unchanged both during rapid citrate infusion (Bunker, Bendixen and Murphy, 1962) and during exchange transfusion in dogs with intact kidneys, TCa increased markedly during citrate infusion in dogs following nephrectomy (Weidner and Clowes, 1960). This increase in TCa, presumably mobilized from skeletal deposits, suggests that the normal animal

may dispose of exogenous citrate by excretion of calcium citrate as well as by hepatic citrate metabolism.

Current recommendations regarding calcium administration during rapid blood transfusion indicate widely divergent views (Howland, Jacobs and Goulet, 1960; Wylie and Churchill-Davidson, 1972; Howland, 1973). While i.v. calcium may improve the inotropic state of the myocardium (Denlinger et al., 1975), excessive doses may cause cardiac arrhythmia. Citrate-induced hypocalcaemia was a transient phenomenon in our patients, suggesting that calcium need not be replaced during rapid transfusion of moderate amounts of citrated blood in healthy anaesthetized man. However, more prolonged hypocalcaemic states requiring large amounts of exogenous calcium have been described recently in critically ill patients (Drop and Laver, 1975). Hypocalcaemia of greater duration requiring calcium replacement may also accompany a massive transfusion in patients with hepatic or renal dysfunction. Hypothermia may prolong citrate-induced hypocalcaemia also (Bunker, Bendixen and Murphy, 1962). Calcium replacement therapy in these critically ill patients may now be based on direct monitoring of Ca^{2+} (Drop and Laver, 1975). A new calcium electrode system (Orion Research, Model SS-20) permits Ca^{2+} analysis within 3 min using heparinized whole blood samples.

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HYPOCALCEMIE PENDANT UNE TRANSFUSION DE SANG A DES HOMMES ANESTHESIES

RESUME

L'administration, à des patients anesthésiés, de sang entier contenant du citrate, pendant 5 min à des taux contrôlés de 50, 100 et 150 ml/70 kg/min a entraîné des diminutions de la concentration des ions de calcium (Ca^{++}), respectivement de 14, 31 et 41%. Après la fin de la transfusion le Ca^{++} est rapidement revenu aux valeurs de contrôle. Il y a eu des changements réciproques dans les concentrations de citrate de sérum, ce qui laisse à supposer que l'hypocalcémie transitoire était due à la redistribution du citrate et au dégagement hépatique ou rénal de l'espace vasculaire. La concentration totale de calcium dans le sérum n'a pas beaucoup changé pendant l'administration rapide de sang. Une infusion saline normale à 100 ml/70 kg/min n'a toutefois pas modifié le Ca^{++} ; l'administration de protéine de plasma à ce taux a entraîné une réduction de 18% du Ca^{++} , probablement par suite de la liaison des ions de calcium aux sites anioniques de la protéine de plasma. L'hypocalcémie qui accompagne la transfusion de sang est un phénomène transitoire, dépendant de la dose totale de citrate administrée et du taux d'infusion. La thérapie rationnelle de remplacement du calcium pendant la transfusion massive de sang pourrait maintenant être basée sur la mesure directe du Ca^{++} .

HYPOCALCÄMIE (KALZIUMMANGEL) BEI BLUTTRANSFUSION AN NARKOTISIERTEN PATIENTEN

ZUSAMMENFASSUNG

Bei narkotisierten Patienten führte die Verabreichung von zitriertem Blut auf die Dauer von 5 min in geregelten Mengen von 50, 100 und 150 ml/70 kg/min führte zu einem Abfall der Kalziumionenkonzentration (Ca^{++}) von jeweils 14, 31 und 41%. Nach Beendigung der Transfusion kehrte Ca^{++} schnell zu den Kontrollwerten zurück. In den Serum-Zitratkonzentrationen kam es zu reziproken Änderungen, was erkennen lässt, dass die vorübergehende Hypocalcämie

ein Ergebnis einer Zitratneuverteilung und einer Leber- oder Nierenentleerung aus dem Gefäßraum war. Die totale Serumkalziumkonzentration änderte sich während der raschen Blutzufuhr nicht auf signifikante Weise. Eine normale Salzinfusion von 100 ml/70 kg/min rief jedoch keine Veränderung von Ca^{++} hervor; Plasmaprotein-Zufuhr derselben Art führte zu einem 18%igen Abfall von Ca^{++} , wahrscheinlich als Folge der Bindung von Kalziumionen an anionische Stellen im Plasmaprotein. Hypocalcämie während Bluttransfusionen ist ein vorübergehendes Phänomen, abhängig von der Gesamtdosis des verabreichten Zitrats und dem Infusionstempo. Rationale Kalzium-Ersatztherapie kann jetzt während massiver Bluttransfusionen auf direkten Ca^{++} -Messungen basiert werden.

HIPOCALCEMIA DURANTE LA TRANSFUSION RAPIDA DE SANGRE AL PACIENTE ANESTESIADO

SUMARIO

En pacientes anestesiados, la administración de sangre entera citrada durante 5 min, a volúmenes controlados de 50, 100 y 150 ml/70 kg/min, resultó en descensos de la concentración del ión cálcico (Ca^{++}) del 14, 31 y 41%, respectivamente. Ca^{++} volvió rápidamente a los valores de referencia una vez concluida la transfusión. Se produjeron cambios recíprocos en las concentraciones de citrato sérico, sugiriendo que la hipocalcemia pasajera fue resultado de redistribución del citrato y del aclaramiento hepático o renal desde el espacio vascular. La concentración total sérica de calcio no cambió significativamente durante la administración rápida de sangre. La infusión salina normal a 100 ml/70 kg/min no causó ningún cambio en Ca^{++} ; la administración de proteína plasmática en igual proporción resultó en un 18% de descenso en Ca^{++} , probablemente como consecuencia de la fijación de iones de calcio a los sitios aniónicos en la proteína del plasma. La hipocalcemia que acompaña a la transfusión de sangre es un fenómeno pasajero, dependiente de la dosis total administrada de citrato y del ritmo de infusión. La terapéutica racional de reposición de calcio durante la transfusión masiva de sangre puede basarse ahora en la medición directa del Ca^{++} .