CHANGES IN IONIZED CALCIUM AND OTHER PLASMA CONSTITUENTS ASSOCIATED WITH CARDIOPULMONARY BYPASS


SUMMARY

Plasma concentrations of calcium fractions, proteins, phosphate and magnesium were measured before, during and after cardiopulmonary bypass in 15 patients undergoing cardiac surgery. When calcium chloride was added to a pump priming solution which contained little or no blood, the concentrations of all calcium fractions were significantly greater after bypass than before, with a mean ionized calcium concentration of 1.52 mmol litre\(^{-1}\) plasma water, 30 min after completion of bypass. This iatrogenic hypercalcaemia was increased significantly by the administration of more than 10 mg kg\(^{-1}\) calcium chloride in the first 30 min after bypass. Other plasma constituents showed the dilutional effect of the pump prime during bypass and only the magnesium concentration failed to return towards normal values after operation.

The importance of calcium in the process of cardiac muscle contraction (Ringer, 1883) and its use as an inotropic agent (Feinberg, Boyd and Katz, 1962) is well recognized. The ionized fraction of the total calcium in plasma is the physiologically active component (McLean and Hastings, 1934). The advent of accurate biochemical (Rose, 1957; Varghese, 1973) and potentiometric (Moore, 1970) methods, rather than relatively crude physiological techniques (McLean and Hastings, 1935), for measurement of ionized calcium have stimulated a renewed interest in monitoring concentration changes during procedures where this ion is likely to be influenced by therapy, as during cardiopulmonary bypass. The plasma ionized calcium concentration after bypass has been found to be either decreased or maintained in the normal range by the administration of large amounts of calcium salts (Das et al., 1971; Johnston et al., 1972; Killen et al., 1972; Moffitt et al., 1973). However, this use of calcium has continued despite the omission of blood from pump priming fluids and the use of citrate–phosphate–dextrose (CPD) blood in preference to acid–citrate–dextrose (ACD) blood in maintaining blood volume. The former contains less citrate to bind ionized calcium (Collins, 1974). It was felt, therefore, that a reappraisal of calcium usage should be undertaken.

METHODS

Fifteen patients (aged 3–64 yr) undergoing cardiac surgery for congenital, rheumatic or ischaemic heart disease were studied. Following premedication with papaveretum, hyoscine and, in some cases, droperidol, anaesthesia was induced with thiopentone and neuromuscular blockade provided by pancuronium. Following endotracheal intubation the lungs were ventilated with a mixture of nitrous oxide in oxygen, and analgesia was supplemented by papaveretum or phenoperidine given i.v. Artificial ventilation was continued for a variable period after operation.

During and after surgery, radial artery pressure, superior vena cava pressure, e.c.g., oesophageal and rectal temperatures and urine output were monitored continuously. During cardiopulmonary bypass, all patients were perfused via a cannula in the ascending arch of the aorta by means of a roller pump; the circulating fluid was oxygenated in a disposable bubble oxygenator.

The priming fluid consisted of 2 litre of Hartmann’s solution, to which was added 8.4% sodium bicarbonate 20 mmol, calcium chloride 250 mg and mucous heparin 3000 i.u. (1 in 1000 solution). For patients with a surface area of less than 1 m\(^2\), a larger amount of calcium chloride (300 mg) was added to the priming solution as CPD blood formed part of the prime and a smaller volume of Hartmann’s solution or Human Plasma Protein Fraction was used. This applied to the two youngest patients in this study.

Before bypass i.v. infusion comprised Hartmann’s solution, except in two adult patients, in whom acute blood loss was greater than 20% of the calculated
blood volume and less than 400 ml of CPD blood was infused. Additional fluid during bypass consisted of Hartmann's solution, and after completion of bypass, all patients received CPD blood, warmed to 37 °C, to maintain blood volume. After bypass, calcium chloride 250–500 mg was given as an inotropic agent and 100 mg was given with each 500 ml of CPD blood.

All patients were cooled to 30–32 °C during part of the bypass. Arterial blood-gases, acid–base status and potassium concentrations were monitored routinely. Arterial blood samples were taken (1) soon after induction of anaesthesia and before bypass, (2) 30 min after commencing bypass, (3) 30 min, (4) 60 min, (5) 4 h, (6) 20 h after completion of bypass. In each case, 20 ml of blood was drawn into a syringe, the deadspace of which had been filled with 1 in 1000 mucous heparin (except during bypass when the patient was heparinized). The syringe was capped so that no air was present, and the stem of the plunger was cut off so that the syringe would fit, nozzle end up, in the pot of a centrifuge. The sample was centrifuged at 1000 g for 10 min. The plasma was transferred anaerobically to a 10-ml syringe which was then capped tightly and placed on ice or stored at 4 °C (Ladenson and Bowers, 1973) until measurements were performed (within 12 h). A small amount of spun plasma was retained to measure osmolality (Advanced Instruments Inc.).

The anaerobically prepared sample was analysed for calcium fractions, proteins, magnesium and inorganic phosphate ions. Ionized calcium in a plasma ultrafiltrate was measured by spectrophotometry using ammonium tetramethylmurexide (Varghese, 1973). Total and ultrafiltrable calcium concentrations were measured by atomic absorption spectrophotometry (IL 453 model atomic absorption spectrophotometer). Total protein was measured by the biuret method (Weichselbaum, 1946). Albumin concentration was measured by the Auto Analyzer method using bromo-cresol green (Northam and Widdowson, 1967). Magnesium concentration was measured by atomic absorption spectrophotometry and inorganic phosphate concentration measured by the Auto Analyzer method N4b. Blood-gas and acid–base measurements were made directly (Radiometer ABL2).

**Statistical analysis**

Two-way analysis of variance was performed for each variable and provided a test of differences between patients and between time intervals. The differences between time differences for calcium fractions, proteins, inorganic phosphate and magnesium were significant at the 5% level. Differences between the means for the control value and samples 2–6 were determined using paired t tests. The differences for plasma osmolality, sodium and potassium values were not significant at the 5% level.

In addition, two sample t tests were performed to identify factors which could influence changes in calcium and other plasma constituents associated with cardiopulmonary bypass. The factors which were assessed in this way were the dose of calcium chloride and rate of blood administration in the 30 min following bypass and the drug therapy before operation.

**RESULTS**

**Calcium fractions (table I)**

The concentration of ionized calcium increased significantly during bypass to a peak at 30 min after completion of bypass; the maximum recorded value was 2.38 mmol litre⁻¹ plasma water. Thereafter, the mean values decreased although remaining significantly greater than the initial values even at 20 h after bypass.

In contrast, the total calcium concentrations decreased significantly during bypass. After bypass, mean concentrations for each sample were greater than initial values, but only significantly so at 1 and 4 h.

Complexed calcium, as with the ionized fraction, increased significantly above initial values until the final sample in which the mean concentrations had decreased and were identical to the initial value. The increase was maximal at 30 min after bypass.

**Proteins (table I)**

There was a profound decrease in plasma proteins, consistent with dilution by the priming volume, at the time of commencing bypass; mean values of both albumin and globulin decreased to 55.6% of initial ones. The concentrations then increased gradually after bypass, although both total protein and albumin concentrations remained depressed in all subsequent samples.

**Phosphate (table I)**

The inorganic phosphate concentration showed no significant change from the initial value except in the first two samples after bypass, when it was found to be significantly increased.
TABLE I. Changes in plasma constituents associated with cardiopulmonary bypass in 15 patients undergoing cardiac surgery. Results are shown as the mean ± SEM and the P values refer to comparison with sample 1.

<table>
<thead>
<tr>
<th>Sample no.:</th>
<th>Before bypass</th>
<th>During bypass</th>
<th>After bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>30 min</td>
</tr>
<tr>
<td>Total calcium (mmol litre⁻¹ plasma water)</td>
<td>2.39 ± 0.03</td>
<td>2.08 ± 0.04</td>
<td>2.72 ± 0.16</td>
</tr>
<tr>
<td>Ionized calcium (mmol litre⁻¹ plasma water)</td>
<td>1.12 ± 0.02</td>
<td>1.21 ± 0.03</td>
<td>1.52 ± 0.08</td>
</tr>
<tr>
<td>Complexed calcium (mmol litre⁻¹ plasma water)</td>
<td>0.22 ± 0.01</td>
<td>0.27 ± 0.02</td>
<td>0.32 ± 0.02</td>
</tr>
<tr>
<td>Total proteins (g litre⁻¹ plasma)</td>
<td>65 ± 1</td>
<td>36 ± 1</td>
<td>44 ± 1</td>
</tr>
<tr>
<td>Inorganic phosphate (mmol litre⁻¹ plasma)</td>
<td>1.11 ± 0.07</td>
<td>0.93 ± 0.06</td>
<td>1.4 ± 0.09</td>
</tr>
<tr>
<td>Magnesium (mmol litre⁻¹ plasma)</td>
<td>1.09 ± 0.04</td>
<td>0.81 ± 0.04</td>
<td>0.82 ± 0.03</td>
</tr>
</tbody>
</table>

Magnesium (table I)

Plasma magnesium concentrations were measured in seven patients. There was a marked decrease after commencing bypass, and the values remained significantly decreased even after 20 h.

Osmolality, sodium and potassium (table II)

Plasma osmolality did not change significantly, although there was a small increase following commencement of bypass. There were also no significant changes in serum sodium and potassium concentrations.

DISCUSSION

The importance of calcium ions in myocardial contractility is well known (McLean and Hastings, 1934, 1935). The availability of an adequate pool of calcium ions in the sarcotubular system, in proximity to the actin-myosin contractile unit, determines the influx during depolarization and therefore the strength and rate of contraction (Langer, 1968; Entman, 1970; Brutsaert, Claes and Goethals, 1973), and largely determines the effectiveness of inotropic agents on the heart (Entman, Levey and Epstein, 1969). There are few situations in which this is more critical than after cardiopulmonary bypass, when effective myocardial contraction is required despite large fluid and electrolyte disturbances and variable periods of induced cardiac arrest or fibrillation, often associated with cooling and the interruption of coronary blood flow.

The first sample (1), taken after induction of anaesthesia and before bypass, was considered as a standard against which to compare subsequent changes. The mean concentrations and standard errors of the calcium fractions in the initial sample are consistent with normal ranges reported elsewhere (Ladenson and Bowers, 1973). The normal range previously established by the method in this study was in healthy active volunteers with a mean ionized calcium of 1.04 mmol litre⁻¹ plasma water and a mean total calcium of 2.51 mmol litre⁻¹ plasma water (Varghese, 1973). The difference between these
and the baseline values found in the patients in this study may be attributed to the fact that the patients were supine for at least 8 h immediately after operation. The change from the supine to the erect posture causes an increase of up to 10% in plasma albumin as a result of a shift of water between body-water compartments (Fawcett and Wynn, 1960; Tarazi et al., 1970) and this is consistent with our initial mean albumin values of 38.3% litre⁻¹ plasma compared with the result in the active normal volunteers of 42.9% litre⁻¹ plasma.

The changes in total and ionized calcium while on cardiopulmonary bypass reflect the effect of a priming solution which contains little or no blood. This effect was seen most dramatically in the profound decrease in plasma proteins, the dilutional effect being confirmed by the same similar percentage decrease in both albumin and globulin concentrations. This decrease in protein concentrations has been observed, to a lesser degree, by other workers (Das et al., 1971; Johnston et al., 1972; Moffitt et al., 1973).

The small but significant increase in the complexed calcium fraction may reflect an increase in plasma lactate (Drop, 1974), both endogenous (Moffitt, Rosevear and McGoon, 1969), and from the pump prime. Significant chelation of calcium by citrate has been observed by Drop (1974), who suggested that significant complexation of calcium can occur during rapid infusion of whole blood.

Thirty minutes after completion of bypass, all the calcium fractions reached the peak value (table I) and in no patient was the ionized calcium concentration less than the value before bypass. To explain these increases, we have considered the possible influences which may be present in the first 30 min after bypass. The most obvious factors are the almost invariable administration of large amounts of calcium chloride as an inotropic agent, and the rapid infusion of CPD blood to maintain blood volume. As can be seen from figure 1, the amount of calcium chloride administered has a distinct effect on the concentration of ionized calcium; when those patients receiving less and more than 10 mg per kg body weight in the first 30 min after bypass were compared, the differences in mean concentrations for the two groups were statistically significant for samples (3) and (4) \( (P = 0.033 \) and 0.021 respectively). The values of

![Figure 1](image-url)  
**FIG. 1.** Effect of calcium chloride administration (mg kg⁻¹) during the 30 min after cardiopulmonary bypass, on mean ionized calcium concentration. Sample 1 before, sample 2 during and samples 3–6 30 min, 1, 4 and 20 h after cardiopulmonary bypass.
complexed and total calcium showed a similar pattern.

Average rates of administration of CPD blood greater or less than 0.5 ml kg\(^{-1}\) min\(^{-1}\) over the first 30 min after bypass did not significantly affect the mean values of ionized or total calcium. The transient decrease and return to normal of ionized calcium concentrations following transfusion of citrated blood has been reported by Hinkle and Cooperman (1971) and Gershonik, Levkoff and Duncan (1973).

Although administration of \(\beta\)-adrenergic blocking drugs before operation had no significant effect on calcium concentrations, there was a significant difference in those patients who had received diuretic therapy, in whom there was a greater increase in ionized calcium after bypass (fig. 2) and this was statistically significant in samples (4) and (5) \((P = 0.046\) and 0.011 respectively). Total calcium concentrations showed a similar pattern although there was no significant effect on complexed calcium. This effect of diuretics may be anticipated when one considers the use of calcium chloride as an inotropic agent at the time of discontinuing bypass. Those patients receiving diuretic therapy before cardiac surgery were presumably in some degree of cardiac failure, albeit controlled, and were more likely to require inotropic support at the end of cardiopulmonary bypass. Five of the six patients receiving high doses of calcium chloride were receiving diuretics before operation.

The addition of CPD blood after bypass helps to restore the plasma protein concentrations and a gradual recovery towards initial values was seen (table I). Some of the increase in complexed calcium immediately after bypass may also reflect the increase in citrate concentrations from the administered blood (Das et al., 1971).

A small but insignificant decrease in phosphate concentrations during bypass may have resulted from dilution and the increase seen in the first two samples after bypass may reflect the administration of phosphate in CPD blood (Collins, 1974), both as part of the CPD anticoagulant and as an accumulation of intracellular phosphate from continued phosphorylation during storage (Schechter and Swan, 1962). An interesting finding was that patients receiving diuretic therapy before operation had a mean initial phosphate concentration of 0.96 mmol litre\(^{-1}\) plasma compared with 1.32 mmol litre\(^{-1}\) plasma in those not receiving diuretics \((P = 0.003)\). The values in the diuretic group remained smaller throughout the series of samples, but only significantly so in sample (5) \((P = 0.011)\).

The importance of magnesium ions in nerve and muscle function has been recognized for some time (Gerst, Porter and Fishman, 1964; Caddell, 1965). The severe depression seen in this study, with possible arrhythmic effects, has been described also by Scheinman, Sullivan and Hyatt (1969) and reflects dilution during bypass and the lack of replacement thereafter. This confirms the need for routine supplements of magnesium when a haemodilution technique is used in cardiopulmonary bypass.

There was an increase in ionized calcium during bypass from the addition of calcium chloride to the pump prime, usually in the absence of citrated blood, and from the profound decrease in plasma protein. This change was aggravated in the period after bypass by the use of additional calcium chloride as an inotropic agent, the salt being almost completely ionized in solution. The use of CPD blood in preference to ACD blood in maintaining blood volume may further aggravate the increase in ionized calcium, since it contains less citrate to bind the ion (Collins, 1974). As a result of this empirical use of calcium chloride, many of the patients became grossly hypercalcaemic at a time when metabolic disturbance is critical.

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**Fig. 2.** Effect of diuretic therapy before operation on mean ionized calcium concentrations in patients undergoing cardiopulmonary bypass. Sample times as for figure 1.
However, there was no clinical evidence of adverse effects in the patients in this study, although several workers describe serious cardiac arrhythmias associated with the administration of large amounts of calcium salt, though these effects have not been related to ionized calcium concentrations (Lloyd, 1928; Hoff, Smith and Winkler, 1939; Wolf, McCarthy and Hafleigh, 1970).

Our study emphasizes the need for closer monitoring of ionized calcium concentrations during and after cardiopulmonary bypass. Without this facility, and with the continued empirical use of calcium chloride, it is apparent that the total amount administered in the critical 30 min after completion of bypass should not exceed 10 mg kg\(^{-1}\). The addition of calcium chloride to the pump prime should be reviewed and the use of calcium with the slow infusion of blood before operation may be considered unnecessary.

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**VARIATIONS DANS LE CALCIUM IONISE ET AUTRES CONSTITUANTS DU PLASMA ASSOCIEES A LA DERIVATION CARDIOPULMONAIRE**

**RESUME**

Les concentrations de fractions de calcium, de protéine, de phosphate et de magnésium dans le plasma ont été mesurées avant, pendant et après dérivation cardiopulmonaire sur 15 malades subissant une intervention chirurgicale à coeur ouvert. Lorsqu'on a jouté du chlorure de calcium à la solution d'amorçage d'une pompe ne contenant que peu de sang ou même pas du tout, les concentrations de fractions de calcium ont été sensiblement plus grandes après la dérivation qu'avant, la concentration moyenne de calcium ionisé dans l'eau du plasma étant de 1,52 mmol litre$^{-1}$, 30 min après la fin de la dérivation. L'hypercalcémie iatrogène a été augmentée d'une manière significative par l'administration de plus de 10 mg kg$^{-1}$ de chlorure de calcium dans les 30 min qui suivent la dérivation. Les autres constituants du plasma ont accusé l'effet diluant de l'amorçage de la pompe pendant la dérivation et seule la concentration de magnésium n'est pas revenue à la normale après l'opération.

**CAMBIO EN EL CALCIO IONIZADO Y OTROS COMPONENTES DE LA PLASMA, ASOCIADOS CON EL PUENTO EXTERNO CARDIOPULMONAR**

**SUMARIO**

Se midieron en la plasma las concentraciones de fracciones de calcio, proteínas, fosfato y magnesio antes, durante y después del puente externo cardiopulmonar en 15 pacientes sometidos a cirugía cardiopulmonar. Cuando se agregó cloruro cálcico a una solución cebadora de bomba que contenía poca o nada de sangre, las concentraciones de todas las fracciones de calcio resultaron significativamente superiores después del puente externo que antes, con una concentración media de calcio ionizado de 1,52 mmol litro$^{-1}$ de agua de plasma, al cabo de 30 min de haberse completado el puente externo. Esta hipercalemia iatrogénica fue aumentada significativamente mediante la administración de más de 10 mg kg$^{-1}$ de cloruro de calcio en los primeros 30 min después puente externo. Otros componentes de la plasma acusaron efectos de la dilución del cebado de bomba durante el puente externo y fue solamente la concentración de magnesio la que no volvió a los valores normales después de la operación.