
Variations of Total and Ionized Calcium Levels During Cardiopulmonary Bypass

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Ionized calcium is essential for many vital functions,¹ some of which are impaired during cardiopulmonary bypass and cardiac surgery:

- Neurotransmission
- Blood coagulation
- Muscle contractility
- Permeability of all membranes and lysosomes
- Release of acetylcholine at motor end-plates
- Cell metabolism—especially oxydative phosphorylation
- Release of various hormones

Cardiopulmonary bypass, with its subsequent hemodilution, has effects on both the total calcium concentration as well as the ionized fraction of calcium. Ionized calcium changes following citrated blood transfusion have been documented.^{2,3,4} This study attempts to analyze ionized and total calcium level variations at many points in the cardiac surgery procedure, as well as the acute effects of blood and calcium chloride administration while on cardiopulmonary bypass.

Methods

In this study of 76 patients undergoing cardiopulmonary bypass, total calcium, ionic calcium, and total protein were determined before induction, immediately

prior to bypass, after established on bypass at hypothermia, prior to termination of bypass, stabilized post-bypass after 1 gram calcium chloride administration, and in ICU on the first post-operative day. Ionic calcium was measured using an ion-selective electrode,^a total calcium was measured using the technique of Baginski et al,⁵ and total protein was measured using the Biuret Reaction Method.⁶

In twelve patients, ionized calcium was measured before and immediately after calcium chloride administration, and in five patients, ionic calcium was measured before and immediately after citrated whole blood was rapidly infused into the extracorporeal circuit.

Results

In this study, ionic and total calcium values were as found on Table I. These results represent a significant decrease in both total and ionic calcium ($p < .05$) from the pre-induction to the two bypass values, with a return to slightly above the pre-bypass values for post-bypass and ICU samples. There were no significant differences between pre-induction and pre-bypass values, nor between the post-bypass and ICU values.

Calcium chloride administration brought on acute changes in ionized calcium from an average value of 1.55 mEq/l to 2.33 mEq/l when measured a few min-

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TABLE I
Ionized and Total Calcium Variations During Bypass

	Ca ⁺⁺ (mEq/L)	S.D.	Ca Total (mg/dl)	S.D.
Pre-Induction	2.04	(.2842)	8.79	(1.191)
Pre-Bypass	2.01	(.2943)	8.44	(1.395)
At Hypothermia	1.73	(.5498)	6.39	(1.281)
Rewarmed	1.64	(.2692)	6.28	(1.170)
Post-Bypass	2.08	(.2745)	8.49	(1.370)
ICU	2.13	(.1141)	8.70	(1.226)

TABLE II
Plasma Protein Levels

	Mean	(S.D.)
Pre-Bypass	6.15 g/dl	(+1.145)
At Hypothermia	3.81 g/dl	(+1.054)
Post-operative	5.94 g/dl	(+1.024)

utes after a 1 gram dose. This represents a 50% increase.

Rapid administration of citrated whole blood acutely decreased the bypass ionic calcium from averages of 1.71 mEq/l to 1.24 mEq/l, a 27% decrease. A return to a normal "rewarmed" value of 1.60 mEq/l was achieved without calcium chloride administration within 15 minutes.

In order to correlate changes in ionized calcium fraction with plasma protein levels, samples were analyzed pre-bypass, at hypothermia, and post-operatively. Results are found on Table II.

These significant changes ($p < .01$) represent a 38% decrease in plasma proteins due to hemodilution with a crystalloid prime. The return to near pre-bypass values reflect hemoconcentration by urine production, blood administration, etc.

Discussion

The clinical importance of calcium ions in myocardial contractility is well known.^{8,9} The strength of contraction of the actin-myosin contractile unit is dependent upon the availability of calcium ions in the sarcotubular system.^{10,11} Normal cardiac function requires a normal level of ionic calcium. The availability of calcium ions determines the effectiveness of inotropic agents.¹² Additionally, calcium is essential for noncardiac functions, such as neurotransmission,

blood coagulation, permeability of all membranes and lysosomes, and non-cardiac muscle contractility.¹

Hypocalcemia has been associated with impairment of cardiac function, reduced vascular tone, neuromuscular irritability, and altered coagulability.^{13,14,15} Causes of hypocalcemia include hemodilution, citrate binding, impaired release of parathyroid hormone (PTH) and inadequate response of calcium reserves to PTH.^{3,4,15,16,18}

Approximately 1% of the total body calcium exists in extravascular fluid, cells and plasma. The remaining 99% occurs in bone and teeth, which provides a large reserve to replenish intravascular levels.¹³ Total extra-cellular calcium is found in three main "compartments": bound to plasma proteins (40%), complexed to such anions as phosphate, sulfate, citrate (10%), and in a free ionized form (50%).^{19,20} It should be stressed that the ionized fraction of the total calcium in plasma is the biologically active component. The three fractions exist in a state of dynamic equilibrium, influenced by three factors: plasma protein levels, pH, and PTH levels. PTH levels are slightly reduced dilutionally, with a return to normal levels within the bypass period.¹⁷ Alkalosis lowers ionized calcium levels 0.04 to 0.08 mEq/l for each 0.1 pH unit increase.^{19,20} As patients in this study maintained normal pH values, effects by this parameter were minimal.

Of principal concern during cardiopulmonary bypass are the dilutional effects not only on the calcium itself, but also on the plasma protein levels, which normally act to buffer ionized calcium concentrations.

The decreases in ionized and total calcium levels with the onset of cardiopulmonary bypass were 14% and 24% respectively. This demonstrates the buffering effect of the plasma proteins. Not surprisingly, when we look at the fraction of ionized calcium, we see an increased fraction while hemodilution has reduced plasma protein values, an important homeostatic mechanism (Table III).

TABLE III
Percent of Total Calcium in Ionized Form

Pre-induction	46%
Pre-bypass	48%
At hypothermia	54%
Rewarmed	52%
Post bypass	49%
ICU	49%

TABLE IV
Ionized/Total Calcium Correlations

Pre-induction	.5711
Pre-bypass	.6454
At hypothermia	<.4
Rewarmed	.6001
Post-bypass	.4803
ICU	<.4

The data show that decreases in total and ionized calcium while on cardiopulmonary bypass may be primarily accounted for by hemodilution with a non calcium-containing prime (Plasmalyte). This is supported by the findings of Gray et al,¹⁷ who noted similar decreases of calcium with hemodilution. In spite of this homeostatic mechanism, serum ionic calcium can be markedly depressed in the presence of normal calcium levels.³

Before the advent of the ion selective electrode for calcium, various formulas have been applied to predict ionized calcium levels from total calcium determinations.^{19,20,22,23} When total calcium levels are "corrected" with total protein, pH, globulins and/or albumin values, substantial correlations can be obtained.^{19,21,22,23} Substantial correlation, however, does not mean good prediction power. Our data provided the correlations found in Table IV. These correlations are consistent with those of Pittinger et al²¹ and with previous research done at this institution.²⁰ While substantial correlations exist, they generally provide poor predictive value. Ionized calcium levels cannot be reliably predicted from other laboratory data.

In our small series of twelve patients who received 1 gram calcium chloride while on bypass, ionized calcium levels increased from a mean of 1.55 mEq/l to 2.33 mEq/l, a 50% increase. It would be expected that the effects of calcium chloride administration would be greater for patients on bypass, due to the dilutional effects on the buffering power of proteins.

The effects of citrated blood infusion on ionized calcium levels have been well studied.^{3,4,24} In our brief look at five patients, ionized calcium levels decreased with rapid administration of citrated blood from an average of 1.71 mEq/l to a very low value of 1.24 mEq/l, a value which may cause problems in myocardial contraction.²⁴ This should be considered when adding citrated blood to the extra-corporeal circuit. Fifteen minutes later, this had increased to an average of 1.60 mEq/l without administration of calcium chloride.

Total calcium levels do not change with citrate infusion. Only the ionic fraction changes.² This again supports the fact that serum ionic calcium levels can be markedly depressed in the presence of normal total calcium levels.^{3,20}

Serum ionic calcium levels decrease in proportion to the volume and rate of citrate infusion.² On bypass, blood is often readily administered. This provides the potential for markedly depressed ionic calcium levels at critical times, especially approaching the termination of bypass. Calcium chloride administration should be considered with the administration of citrated blood at critical stages of bypass, especially when myocardial function is required.

Summary

Ionic and total calcium levels were measured at various stages of cardiac surgery and recovery, and before and after calcium chloride and citrated blood administration.

Ionized and total calcium levels decreased with initiation of bypass, primarily as result of hemodilution. Administration of 1 gram of calcium chloride raised the depressed values to normal levels. Although spontaneous recovery from citrate-induced hypocalcemia will occur with time, infusion of calcium chloride should be considered when citrated blood is rapidly infused at critical times of required myocardial performance.

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