Relationship between Serum Lactate and Ionized Calcium in Open-Heart Surgery

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We studied 16 patients undergoing open-heart surgery and heart–lung bypass, to examine the relationship between ionized calcium and lactate. Blood was sampled at successive stages of the operation for measurement of ionized and total calcium, lactate, blood gases, pH, hematocrit, and other constituents. We found that correlations between ionized calcium and lactate were positive and statistically significant ($p < 0.05$), both among and within patients. The linear regression of ionized calcium on lactate remained highly significant ($p < 0.0001$) after adjustment for variability among patients and across operative stages as well as after correction for pH and hemodilution. The significant regressions between calcium and lactate, both before and after administration of calcium, indicate a relationship for calcium and lactate in patients undergoing open-heart surgery.

Ionized calcium has frequently been studied in patients undergoing open-heart surgical procedures involving heart–lung bypass (1–10). Because of the variation in surgical techniques used for these procedures, and influences such as transfusion of citrated blood, hemodilution by fluids, administration of calcium salts, anesthesia, acid–base changes, body-temperature changes, and administration of heparin and protamine, ionized calcium has been reported to increase (9), decrease (1, 2, 4–6, 8), or change little (2, 3, 7, 8, 10). More consistent data have been reported for blood lactate concentrations during open-heart surgery. Lactate concentrations in serum increase several fold during heart–lung bypass, and may remain above normal for several days afterwards (11, 12), possibly owing to localized tissue ischemia, to decreased liver function from hypoxia, to hypothermia, or to all three. Reportedly, both calcium and lactate increased markedly during exercise, although no relationship between them was discussed (13).

Other studies indicate that infusion of calcium can increase myocardial oxygen consumption and cardiac stroke work (14), and may be a cause of localized tissue necrosis (15), all of which may relate to the production of lactate. In addition, lactate is known to bind calcium (16), which may also affect the concentration of ionized calcium. Most previous work has focused on relationships among ionized calcium, parathyrin, and pH, but the potential contribution of lactate to homeostasis of ionized calcium was not examined. Therefore, we studied 16 patients undergoing open-heart surgery requiring heart–lung bypass, to determine the relation, if any, between ionized calcium and lactate.

Materials and Methods

Patients. We obtained serial blood specimens from 16 male patients undergoing various "open-heart" surgical procedures requiring heart–lung bypass. Twelve of the 16 patients were undergoing coronary artery bypass graft procedures. Of the remaining four patients, three underwent surgery for heart-valve replacement: one for the mitral valve, one for the aortic valve, and one for replacement of both. The remaining patient we studied underwent open-heart surgery for repair of an atrial septal defect.

Open-heart procedure. After the patient has stabilized under anesthesia in the operating room, heparin is administered intravenously to induce sufficient anticoagulation as determined by activated clotting time. After the surgical incision, the arterial and venous systems are cannulated and tubing from the heart–lung pump is connected to the arterial and venous catheters, forming a closed system for maintaining circulatory and gas exchange functions during cardioplegia. For the cases included in this study, the bypass pump was primed with a balanced electrolyte solution containing albumin, potassium, heparin, and mannitol. After activation of the heart–lung pump, a gradual mixing period facilitates accommodation of the patient's system to hemodilution concurrent with transition to extracorporeal circulation.

To diminish metabolic demand in all body organs during open-heart surgery, the patient's body temperature is decreased so as to be within the range of 20–30°C. Before actual surgical manipulation of the heart, cardioplegia is induced by cross-clamping the aorta and infusing a cooled solution containing dextrose and 20–30 mmol of potassium chloride per liter. For the patients included here, the cardioplegic state was maintained for 30 to 90 min.

Upon completion of surgery, the aortic cross clamp is removed and the cardioplegic fluid is purged, thereby restoring mechanical activity of the heart. Subsequently, as vital functions are carefully monitored, the patients can be weaned from extracorporeal circulation by gradual occlusion of tubing to the heart–lung pump. After decannulation, protamine sulfate is administered to inactivate the anticoagulation effects of heparin. Calcium chloride is also administered at this time to offset the hypotensive effects of protamine. To counterbalance the patient's hemodiluted state, transfusion of blood products consisting of packed erythrocytes and fresh frozen plasma may also be given. Each unit of packed cells had 1 g of calcium added, as calcium chloride.

Heart–lung bypass staging. To normalize the cases included in this study, we staged each heart–lung bypass procedure, using criteria similar to those described by Chambers et al. (3), viz Stage 1 is the preoperative period shortly after each patient was anesthetized; Stage 2 is just prior to bypass surgery after administration of heparin for anticoagulation, Stage 3 is during heart–lung bypass; Stage 4 is at the end of heart–lung bypass; and Stage 5 is the postoperative period subsequent to intravenous administration of protamine, calcium, and transfusion of blood products.
Sampling. During each stage of each open-heart procedure, 10 mL of each patient's heparinized blood was obtained by syringe, capped, and immediately delivered on ice to the laboratory. From this sample, aliquots were promptly analyzed for lactate and blood gases. The remaining sample, approximately 5 mL, was used in analysis for total calcium, ionized calcium, and albumin. A few patients could not be sampled at all operative stages, particularly at Stage 4 near the end of bypass, owing to technical complications.

Blood-gas determination. For determination of pH, PCO₂, and PO₂, we used the 188 pH/Blood Gas System (Corning Medical, Medfield, MA 02052), following the manufacturer's instructions. All pH, PCO₂, and PO₂ determinations were corrected for effects of patient temperature and hemoglobin by the method described by Kelman and Nunn (17).

Ionized-calcium instrumentation. We used the Nova 8 system (Nova Biomedical, Waltham, MA 02254), following the manufacturer's instructions, to measure ionized calcium at 37 °C in blood specimens included in this study.

Lactate analysis. We measured lactate concentration in serum with the Du Pont aca system (Du Pont, Wilmington, DE 19888). Methodology for this system is based on monitoring, at 340 nm and 383 nm, the reduction of NAD⁺ during conversion of lactate to pyruvate catalyzed by lactate dehydrogenase (EC 1.1.1.27).

Total calcium and albumin measurements. We determined concentrations of total calcium and albumin in all serum specimens by dry-slide technology with the Ektachem (Eastman Kodak Co., Rochester, NY 14650). The Ektachem system used Arsenazo III, at pH 5.6, and brom cresol green to form dye complexes with calcium and albumin, measurable by reflectance spectrometry at 680 nm and 630 nm, respectively.

Statistical methods. Regression and correlation techniques were utilized to assess the relationships among ionized calcium, lactate, and other measured variables. Data plots over successive stages of the operation were empirically examined for each patient, and the linear correlation between ionized calcium and lactate was also estimated and tested for statistical significance. Within-patient correlations were combined into a single estimate and tested for heterogeneity by the method of Fisher (18). Data stratified by the stage of operation were used to estimate univariate statistics as well as bivariate correlations among patients. In order to delineate average patterns and pertinent changes in variable relationships during the course of the operation.

Finally, an analysis of covariance of all ionized calcium data was performed in a two-way classification model with patients and operative stages as classification factors and hemocrit, pH, and lactate as the covariates (18). The covariable lactate was fitted last in the model, in order to estimate and test the significance of the linear regression of ionized calcium on lactate after adjustment for possible average effects of patients and operative stages as well as correction, by linear regression, for effects of pH and hemo dilution (as gauged by the hematocrit). This analysis was also utilized to partition the variability due to linear regression of ionized calcium on lactate among patients and test the heterogeneity of regression among patients.

Results

Figure 1 shows plots of each patient's ionized calcium and lactate concentrations across stages of the operation. Empirical inspection of Figure 1 reveals a general positive association between these two variables, which is supported statistically by positive correlation coefficients in 12 of the 16 patients, and a significant positive combined estimate of within-patient correlation ($r = 0.55$, $p < 0.01$). Furthermore, a test for heterogeneity of within-patient correlations did not approach statistical significance ($p < 0.25$).

Table 1 summarizes the mean changes in calcium, lactate, pH, and hematocrit at each stage of the operation, along with the correlation coefficients between ionized calcium and lactate among patients. Despite hemodilution, as indicated by the generally declining hematocrit values and decreasing concentrations of albumin (not shown) throughout surgery, ionized calcium decreased only slightly between operative Stages 1 and 2, and then increased during Stages 2 through 5. Similarly, lactate increased across all stages of surgery. These linear trends in ionized calcium and lactate show high statistical significance ($p < 0.01$) and contrast markedly with fluctuations in temperature-corrected pH, which reflect mild alkalemia in Stages 2–4 and slight acidosis in Stage 5; they also differ from the pattern for total calcium, which is relatively low in Stages 2-4 and then increases dramatically concurrent with infusion of calcium in Stage 5. The ratio of ionized calcium to total calcium is significantly increased in Stages 3 and 4 relative to Stage 1 and 2 ($p < 0.001$), coincident with the increasing ionized calcium and declining total calcium.

Ionized calcium correlated well with lactate among the patients represented at every stage, but especially at Stage five after patients had been weaned from bypass and calcium was administered (Table 1). Because of the strong correlation at stage five, we looked at changes, by patient, in
ionized calcium and lactate that resulted from the initial administration of calcium. The data in Table 2 indicate that, in all but three of the 16 patients, the changes in ionized calcium and lactate were in the same direction. Four patients showed a concurrent decrease in ionized calcium and increase in total calcium, probably because of excess citrate in blood products they received, as discussed later.

Table 3 shows results of the analysis of covariance of ionized calcium, with patients and operative stages used as classification factors and hematocrit, pH, and lactate as covariates. As expected, there is significant variability in ionized calcium among patients and across operative stages, as indicated by the statistical significance of the corresponding mean squares. Notably, the linear regression of ionized calcium on lactate is highly significant (p <0.0001), even after allowance for the average effects of patients and operative stages, as well as adjustment for linear regression of ionized calcium on pH and hematocrit. Furthermore, variability due to heterogeneity of the regression of ionized calcium on lactate does not reach statistical significance (p <0.16), indicating that a single regression line is adequate. Based upon the estimated regression coefficient, for the average patient studied with pH and hematocrit held constant at their mean values, each millimole per liter increase in lactate is associated with an approximately 0.1 mmol/L increase in ionized calcium.

A few patients exhibited substantial increases in both lactate and ionized calcium after transfusion of blood products in operative Stage 4 (Figure 1). To determine if these post-transfusion data from Stages 4 and 5 may have produced a fortuitous relationship between ionized calcium and lactate, we examined separately the pre-transfusion data of Stages 1–3, using the same analysis of covariance format of Table 3. This analysis corroborated the significant regression (p <0.02) of ionized calcium and lactate, even after adjustment for the covariates hematocrit and pH (Table 3).

**Discussion**

Our study shows that changes in lactate concentrations in patients undergoing open-heart surgery with heart–lung bypass correlate significantly with ionized calcium, both before and (especially) after coadministration of calcium with protamine or citrated blood. Mean values for both ionized calcium and lactate showed generally linear increases during surgery despite hemodilution and fluctuating pH, whereas total calcium remained low until the post-bypass operative Stage 5, when exogenous calcium and blood products typically were infused (Table 1). Correlations between ionized calcium and lactate among patients were positive and statistically significant (p <0.05), or nearly so, at every stage of open-heart surgery (Table 1), and within-patient correlations were positive in most patients. Results of the analysis of covariance across all patients and operative stages showed that the linear regression of ionized calcium on lactate remained at an extremely high level of significance (p <0.0001), even after adjustment for among- and within-patient variability as well as correction for effects of possible confounding factors such as pH and hemodilution (Table 3).

Data published by Aloia et al. (13) reveal a significant correlation between average concentrations of ionized calcium and lactate during exercise-induced mild hypercalcemia.
However, these authors did not discuss this relationship, and concluded that hemoconcentration was responsible for the increased ionized calcium, although other studies (19, 20) have shown that hemoconcentration per se has little effect on ionized calcium. In another such study (12), similar changes in ionized calcium and lactate were observed. Although these authors (12) concluded that the concurrent decrease in blood pH was partly the cause of the increase in ionized calcium, their results indicated that some other in vivo factor may have contributed to this increase.

In the current study, we also observed a significant relationship between calcium and lactate, both across all operative stages (p < 0.001 in Table 3) and for Stages 1–3, before any calcium or blood products were administered (p < 0.02 in Table 3). However, we demonstrated by an analysis of covariance that this relationship cannot be accounted for solely by change in pH or hemoconcentration, suggesting that lactate may facilitate an increase in ionized calcium, or vice versa. Further, examination of the value for ionized calcium and lactate, as well as the ratios of ionized to total calcium, shows that substantial average increases occurred in all of these variables during open-heart surgery prior to administration of calcium or transfusion of citrated blood products (Table 1). These data therefore provide evidence that calcium homeostasis is altered by lactate production, or vice versa, relatively independent of pH or hemoconcentration.

Several reports indicate that administration of calcium may enhance oxygen consumption, which could lead to tissue hypoxia and, consequently, an increase in production of lactate. Infusion of calcium increases cardiac stroke work, thus increasing oxygen demand (14). Because calcium ions also have a role in triggering glycogenolysis (21), calcium may influence the production of lactate through its effect on energy utilization during muscle contraction. At least two groups of investigators have reported the occurrence of tissue necrosis localized at the site of calcium injection in neonates (22, 23). The mechanism of the necrosis was not known, but calcium was believed to be the causative agent.

In our study, calcium was given by bolus injection, usually near the end of the surgical procedure. As shown in Table 2, the direction of change in lactate and ionized calcium was the same in 12 of the 15 patients from whom samples were collected before and after calcium administration. These results, coupled with the highly significant correlation between ionized calcium and lactate at Stage 5 after infusion of calcium (r = 0.81, p < 0.001), suggest that administration of calcium somehow accentuated the association between these variables. As patients are weaned from cardiopulmonary bypass at Stage 4, the myocardium is in a weakly contractile state, which may lead to inadequate tissue perfusion, hypoxia, and production of lactate. Because the patient is usually mildly hypocalcemic, calcium is given to improve hemodynamic function, thereby creating an increased demand for oxygen, which could lead to the increased production of lactate. However, other mechanisms are also plausible. For example, the warming of patients after bypass coincided with the administration of calcium. Warming can lead to an increased production of lactate, so this may explain, at least in part, the enhanced correlation between ionized calcium and lactate. Another possible interpretation involves the ischemic conditions of the heart during bypass. A considerable accumulation of myocardial lactate could result from cardioplegia and be introduced into circulation upon reactivation of the heart and weaning from the heart–lung machine in the same time frame as calcium administration. This scenario could produce concurrent spurious increases in both variables. However, contradictory to the latter two proposed mechanisms are that four patients showed decreases in both ionized calcium and lactate during Stage 4, and that ionized calcium and lactate were significantly related (p < 0.02) before any calcium or blood products were administered.

Most of our patients received citrated blood products to counterbalance their hemodilute state, typically after weaning from the heart–lung bypass pump. As noted previously, four patients had a concurrent decrease in ionized calcium and lactate, with an increase in total calcium, during transfusion of blood products. This probably is ascribable to an excess of citrate in some units of blood, which would bind calcium when transfused.

Based on our results, hemoconcentration or changes in pH, or both, cannot readily be advanced as an explanation of the observed pattern of ionized calcium. Even though no calcium was given in Stages 1–3, ionized calcium increased despite decreases in albumin, hematocrit, and total calcium and a corresponding increase in pH. While it is tempting to explain this increase in ionized calcium as being due to parathyrin-induced release of calcium from bone, parathyrin apparently does not rapidly increase concentrations of ionized calcium in blood (24, 25).

If the affinity between albumin and calcium could be decreased during hypocalcemia, it would be a mechanism to quickly offset hypocalcemia, as has been speculated before (25–27). The association that we observed between lactate and ionized calcium is consistent with the hypothesis that lactate alters this affinity. Further investigations need to focus on this relationship by measuring ultrafiltrable calcium in order to calculate the protein-bound calcium and determine if the association constant between calcium and albumin changes during conditions of hypocalcemia and lactate production.

References