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Hypocalcemia Following Resuscitation from Cardiac Arrest Revisited

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Abstract

Objective—Hypocalcemia associated with cardiac arrest has been reported. However, mechanistic hypotheses for the decrease in ionized calcium (iCa) vary and its importance unknown. The objective of this study was to assess the relationships of iCa, pH, base excess (BE), and lactate in two porcine cardiac arrest models, and to determine the effect of exogenous calcium administration on postresuscitation hemodynamics.

Methods—Swine were instrumented and VF was induced either electrically (EVF, n=65) or spontaneously, ischemically induced (IVF) with balloon occlusion of the LAD (n=37). Animals were resuscitated after 7 minutes of VF. BE, iCa, and pH, were determined prearrest and at 15, 30, 60, 90, 120 min after ROSC. Lactate was also measured in 26 animals in the EVF group. Twelve EVF animals were randomized to receive 1 gm of CaCl₂ infused over 20 min after ROSC or normal saline.

Results—iCa, BE, and pH declined significantly over the 60 min following ROSC, regardless of VF type, with the lowest levels observed at the nadir of left ventricular stroke work post resuscitation. Lactate was strongly correlated with BE ($r = -0.89$, $p < 0.0001$) and iCa ($r = -0.40$, $p < 0.0001$). In a multivariate generalized linear mixed model, iCa was 0.005 mg/dL higher for every one unit increase in BE (95% CI 0.003–0.007, $p < 0.0001$), while controlling for type of induced VF. While there was a univariate correlation between iCa and BE, when BE was included in the regression analysis with lactate, only lactate showed a statistically significant relationship with iCa ($p = 0.02$). Postresuscitation CaCl₂ infusion improved post-ROSC hemodynamics when compared to saline infusion (LV stroke work control 8 ± 5 gm-m vs 23 ± 4 , $p = 0.014$, at 30 min) with no significant difference in tau between groups.

Conclusions—Ionized hypocalcemia occurs following ROSC. CaCl₂ improves post-ROSC hemodynamics suggesting that hypocalcemia may play a role in early post-resuscitation myocardial dysfunction.

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Keywords

cardiac arrest; hypocalcemia

INTRODUCTION

Postresuscitation myocardial dysfunction and hypotension are components of the postresuscitation syndrome⁽¹⁾ ascribed to transient stunning of the myocardium.⁽²⁾ Myocardial injury caused by electrical shocks and the administration of epinephrine may be contributing factors.^(3,4)

Ionized calcium is known to play a role in myocardial contraction as well as smooth muscle tone of the peripheral vascular bed.^(5,6) Acute hypocalcemia is associated with a type of heart failure which may be ameliorated with intravenous calcium.^(7–9) Ionized calcium levels decrease during cardiac arrest or shortly after the return of spontaneous circulation,^(10–13) the magnitude depending on the duration of cardiac arrest.

Despite the well documented occurrence of resuscitation-related ionized hypocalcemia, its potential importance has not been evaluated, nor has its utility as a therapeutic ever been demonstrated in this setting.⁽¹⁴⁾ The purpose of this study was: 1. to assess the relationship between arterial pH, base excess, lactate and ionized calcium following resuscitation from cardiac arrest in a porcine model and, 2. to determine the effect of calcium administration in the early postresuscitation period on myocardial function.

METHODS

These studies were approved by the Animal Care and Utilization Review Committee of our institution and conformed to the position of the American Heart Association on research animal use.

Arterial pH, Base Excess, Lactate and Ionized Calcium Following Resuscitation

During studies in our laboratory comparing electrical and ischemically induced VF and resuscitation in 102 swine,^(15–19) arterial blood gases and ionized calcium were obtained at pre-designated intervals. Arterial lactate was measured in a subset of 26 of the electrically induced VF animals to further characterize physiologic relationships in the early post-resuscitation period. Study design, instrumentation, and measurements have been previously reported. ^(16–19)

In brief, domestic mixed Yorkshire swine (n=102) of either sex and weighing 32–48 kg were premedicated and general anesthesia maintained with inhaled isoflurane and nitrous oxide in a 1:1 mixture with oxygen. End tidal CO₂ was continuously monitored and minute ventilation adjusted to maintain a value of 35–45 mmHg. Standard lead II of the surface electrocardiogram was monitored throughout the study.

Vessels were surgically exposed and, under fluoroscopic guidance, high fidelity, micro-manometer tipped catheters (Millar Instruments, Houston, TX) were inserted and positioned in the right atrium (RA), left ventricle (LV), and aortic arch (Ao). A multilumen catheter thermistor (Edwards Lifesciences, Irvine, CA) was positioned in a branch of the pulmonary artery.

Following instrumentation, hemodynamic variables were measured or calculated and arterial blood was analyzed (I-Stat CG8+, I-Stat Corp, Princeton, NJ). Electrocardiographic and

hemodynamic data were continuously recorded onto a laptop computer utilizing PowerLab Chart acquisition software (v. 5.2, ADInstruments, Castle Hill, Australia).

VF was electrically induced (EVF, n=65) or ischemically induced (IVF n=37). EVF was induced via a standard 7-F bipolar pacing catheter in the apex of the right ventricle endocardium. For IVF, a standard percutaneous transluminal coronary angioplasty was used to occlude the left anterior descending coronary artery with cessation of coronary flow confirmed by manual contrast injection under fluoroscopy.

After 7 minutes of untreated electrical or ischemic VF, mechanical closed-chest compressions (Thumper, Michigan Instruments, Grand Rapids, MI) were begun. In the ischemic group the occluding balloon remained inflated throughout resuscitative efforts. One minute after starting chest compressions, a transthoracic biphasic countershock at 200J was given (LifePak 12, Physio-Control Corporation, Redmond, WA). If VF persisted, advanced cardiac life support (ACLS) was continued per guidelines.(20) At the end of 15 mins of ACLS, animals remaining in VF, PEA, or asystole were considered resuscitation failures and resuscitative efforts terminated.

In those animals achieving restoration of spontaneous circulation (ROSC), defined as an arterial systolic pressure >60 mm Hg for at least 10 min,(21) hemodynamic and blood gas measurements were continued at intervals for 3 to 6 hrs. Specifically, base excess (BE), ionized calcium (iCa), and pH, were determined prearrest and at 15, 30, 60, 90, and 120 min after ROSC and then at hourly intervals for a total of 6 hours. Arterial lactate (iStat CG4+, I-Stat Corp, Princeton, NJ) was measured in 26 of the EVF animals at the same time as BE, pH, and iCa was measured prearrest and at the 15, 30, and 60 min time points.

Blood samples were collected in minimally-heparinized plastic syringes and analyses completed within 7 min of sampling. Ionized calcium concentrations were not corrected for pH, protein, or albumin levels. All animals received 1.5 to 2 L of normal saline over the duration of the experiment.

Effect of Postresuscitation Calcium Administration

To determine if ionized hypocalcemia plays a role in postresuscitation myocardial dysfunction, 12 additional animals were instrumented as described above. VF was induced electrically, resuscitation accomplished, and measurements made as above. Following resuscitation, animals were randomized by permuted block design to receive either an infusion of 1 gm of calcium chloride in 250 ml of normal saline (6 animals) or 250 ml of normal saline (6 animals). Infusions were begun 5 min after ROSC and completed over 30 min. Hemodynamic measurements were made and blood sampled prearrest and at 15, 30, 60, 90, and 120 min.

Data Analysis

All statistical analyses were conducted using SAS Version 9.1.3 (SAS Institute, Cary, NC). Summary measures are reported as means and standard deviations for normal distributions. Pearson correlations were used to estimate correlations between normally distributed variables and Spearman rank correlations used for non-normally distributed variables. One-way repeated measures ANOVA, Student's t-test, or Mann-Whitney Rank Sum were used for hemodynamic comparisons between saline and calcium chloride treated animals.

Generalized linear mixed models were employed to evaluate associations between variables while accounting for the autocorrelation inherent in repeated measure designs. The SAS procedure, Proc Mixed, was employed for this purpose, with time included as a random effect and other variables included as fixed effects. Variable selection was based on a priori assumptions and iterative fitting of potential models. Model fit and correlation structure

specification was assessed by Akaike Information Criteria. Measures of influence, using the SAS model option “INFLUENCE” were inspected for identification of potentially influential cases. Models were then refitted after single-animal deletions of such potentially influential cases. We chose to identify potentially influential animals rather than individual observations since the sampling unit in linear mixed models is the subject from whom measurements are drawn. We considered an alpha level of 0.05 to be significant.

RESULTS

Table 1 includes control hemodynamic variables for IVF and EVF animals.

Ionized calcium levels in the post-resuscitation period

In the post-resuscitation period, iCa declined significantly within 30 min in both electrically and ischemically induced animals (Figure 1). While iCa among EVF animals recovered by 120 minutes, iCa in IVF animals did not recover until 180 minutes post-resuscitation. GLM modeling, using a quadratic change trajectory in which time and its squared value are included in the model (to model curvature in the iCa response), demonstrated a significant difference in iCa levels between the two VF groups during the first 180 minutes post-resuscitation. During this period, iCa was, on average 0.05 mmol/L lower in IVF animals (95% confidence interval: 0.02 to 0.07 mmol/L lower, $p=0.001$) when compared to EVF animals. There was furthermore a statistically significant slower decline, as well as faster recovery, in the ionized calcium response among EVF animals when compared to IVF animals by 0.0005 mmol/L/minute (95% CI 0.0001 to 0.001 mmol/L/minute, $p=0.01$). After 180 minutes, no statistically significant difference in iCa was seen between VF groups.

Base Excess and pH levels in the post-resuscitation period

Similarly, both BE and pH were lower in IVF vs. EVF animals following resuscitation, 5.90 units (95% CI 4.10 to 7.68 units, $p<0.0001$) lower, on average for BE and 0.063 units (95% CI 0.035 to 0.091 units, $p<0.0001$) lower, on average for pH. Both values reached their nadir at 60 minutes before beginning to recover. There was a difference in the slope of the BE response curve with EVF animals having a slower decline and faster recovery by 0.054 units/minute (95% CI 0.031 to 0.077 units/minute, $p<0.0001$).

Associations between ionized calcium and other variables

The univariate correlations between hematologic measures of interest are shown in Table 2.

Arterial pH was associated with the post-resuscitation iCa response in GLM modeling. iCa increased by 0.0133 mmol/L (95% CI 0.0021 to 0.0246 mmol/L, $p=0.02$) for every standard deviation increase in pH (sample standard deviation of 0.09), while controlling for type of VF induction (EVF vs. IVF). In similar fashion, BE was found to predict iCa levels, while controlling for type of VF. For every one unit rise in BE, iCa rose, on average, by 0.0050 mmol/L (95% CI 0.0031 to 0.0069, $p<0.0001$).

In the subset of 26 EVF animals in whom lactate was measured, values of lactate rose significantly and plateaued over the first 30 minutes post-resuscitation (Figure 2). In a fitted model, this rise in lactate was closely associated with BE levels, on the order of an average decline in BE of 3.03 units (95% CI 1.78 to 4.28, $p<0.0001$) for every one hundred percent increase in the value of lactate from its prearrest value (time=0).

Lactate and iCa were also associated. A fitted model predicted that iCa, on average, decreased by 0.056 mmol/L (95% CI 0.033 to 0.080, $p<0.0001$) for every one hundred percent increase in the value of lactate. Single animal deletions of potentially influential cases caused variation

in the magnitude of the lactate-iCa association, as displayed graphically in Figure 3, while the direction of association and its statistical significance remained unchanged.

Given the high correlation between lactate and BE, we were uncertain whether controlling for the effects of BE might unintentionally control for the effects of lactate at the same time. Variance inflation factors for BE and lactate were calculated using exploratory linear regression models and found to be nearly five (4.94 and 5.09, respectively), where values of >5 suggest potential problems with multi-collinearity. Nevertheless, when BE was included in the model with lactate, lactate was still significantly associated with the iCa response, while BE was not ($p=0.53$). The fitted model predicted that iCa decreases by 0.046 mmol/L (95% CI 0.006 to 0.086 mmol/L decrease, $p=0.02$) for every one hundred percent increase in the value of lactate, when base excess is held constant. Results obtained while controlling for pH rather than BE were similar. In this model, iCa was predicted to decrease by 0.085 mmol/L (95% CI 0.051 to 0.119 mmol/L decrease, $p<0.0001$) for every 100% increase in lactate.

Hemodynamic response to calcium chloride

Resuscitation variables for the placebo and calcium chloride infusion groups are shown in Table 3. Significant differences were not observed for those variables likely to affect post-resuscitation myocardial function.

Mean arterial pressure and left ventricular stroke work for the study groups are shown in Figure 4. Significant differences between groups were observed 30 min after resuscitation. Tau for the two groups was not different during the 2 hour postresuscitation observation period. Ionized calcium in the control group was less than prearrest values at all time points during observation and a significant positive association was observed between ionized calcium level and left ventricular stroke work ($r = 0.78$, $p < 0.0001$). In the treatment group, a small but significant increase above control group iCa values was observed at 30 min (1.50 vs 1.14, $p<0.001$) and at 60 min (1.37 vs 1.16, $p<0.001$) sampling times.

DISCUSSION

In this study, a decrease in ionized calcium was consistently observed following resuscitation from VF arrest with a nadir predictably occurring 30 min after ROSC. Its decline was associated with the rise in lactate and its nadir coincided with the nadir of myocardial dysfunction as reflected in left ventricular stroke work. Calcium administration following ROSC attenuated this decrease in myocardial dysfunction and maintained mean arterial pressure above 65 mmHg, a typical threshold for pressor treatment. Isovolumetric relaxation time (tau) was not affected by calcium therapy, suggesting that administered free calcium did not cause ischemic contracture.

The relationship between BE and lactate is likely complex, and results should be interpreted cautiously. We chose to control for BE rather than pH in analyzing the lactate-ionized calcium relationship as the former is a derived variable and contains information on both measured pH and pCO_2 . However, control of pH alone did not alter the results substantially.

Urban and colleagues first documented ionized hypocalcemia during cardiac arrest and resuscitation.⁽¹⁰⁾ In their study, a single blood sample was drawn upon hospital arrival of patients with out-of-hospital cardiac arrest. An inhospital cardiac arrest group, predominantly post-surgical patients, was also included in their analysis. The authors reported a significant correlation between ionized calcium and pH. Lactate was not measured and 70% of the out-of-hospital arrest group received intravenous sodium bicarbonate prior to calcium determination. The investigators hypothesized that the observed decrease in ionized calcium was due to extracellular complexing.

Differences in ionized calcium between arterial and mixed venous blood during CPR in patients were not observed by Gando et al.(11) They also reported that lower calcium levels were observed with increasing CPR duration and that ionized calcium levels were not significantly different between those patients who achieved ROSC and those that did not. The authors postulated that the observed decrease in ionized calcium was due to cellular uptake and sequestration during ischemia. Of note, ionized calcium was not directly measured but calculated based upon total serum calcium and measured pH. Relationships between pH and ionized calcium were not assessed statistically.

Cairns et al reported a significant correlation between ionized calcium levels and lactate but not pH in prolonged VF and resuscitation in a canine model.(12) By design, sodium bicarbonate was not given and ventilation was controlled.

In a subsequent clinical study, Gando and coworkers measured ionized calcium as well as pH, bicarbonate, lactate, and pyruvate in patients with out-of-hospital cardiac arrest.(13) Resuscitation efforts included administration of sodium bicarbonate. Blood samples were obtained shortly after hospital arrival and again at termination of resuscitation efforts or at 30 min and 60 min after arrival for those patients with ROSC. In neither group was a relationship demonstrated between ionized calcium and lactate. A significant correlation was observed in non-resuscitated patients between ionized calcium and pH and ionized calcium and bicarbonate. In resuscitated patients, a relationship was demonstrated between ionized calcium and pH. The investigators again suggested that the decrease in ionized calcium observed during and after resuscitation was related to intracellular influx.

The differences in results between the clinical study by Gando (13) and the present study may be explained by several factors. In our animal model, ventilation was strictly controlled and sodium bicarbonate not given during resuscitation. The timing of blood samples with respect to onset of arrest and ROSC is likely more variable in a clinical sample characterized by uncertainty with respect to downtime and return of circulation. Most of the variation in ionized calcium and lactate observed in our study occurred between the prearrest and early post-resuscitation period. Prearrest values were not measured in Gando's study, thus leaving values that were likely at or near their nadir (or peak in the case of lactate) for analysis. Furthermore, our method of analysis employed generalized linear mixed modeling, which is a more recent and robust method for the analysis of time-dependent change trajectories. Not unlike Gando, we observed persistent ionized hypocalcemia over the 60 minutes following resuscitation in IVF animals, a method of induction most similar to the pathogenesis of the majority of adult cardiac arrest. In the subgroup of EVF animals in which lactate was measured, we observed an early rise in lactate over the first 15–30 minutes that remained elevated for at least 60 minutes. Gando also noted persistent lactate elevation 60 min after hospital arrival.

The potential effects of ionized hypocalcemia occurring during or after resuscitation have not been evaluated. Our analysis includes only animals that achieved ROSC. In these animals, we observed a significant relationship between ionized calcium and left ventricular stroke work. These findings suggest that a fall in ionized calcium may play a role in early post-resuscitation myocardial dysfunction. The infusion of calcium chloride significantly increased mean arterial pressure and left ventricular stroke work, had no significant effect on tau, and resulted in only a small but statistically significant increase in ionized calcium, an increase dramatically less than the abrupt rise in total calcium reported after bolus calcium chloride administration.(22)

The administration of calcium during cardiac arrest and following reperfusion is not without theoretical adverse effect. During ischemia, cellular uptake of calcium, largely due to altered membrane transport, has been consistently demonstrated.(23) Intracellular and mitochondrial calcium overload during ischemia has been linked to apoptosis.(24) However, reperfusion

injury typically occurs shortly after restoration of blood flow, demonstrated by a burst in reactive oxygen species within seconds of reperfusion.(25–26) The role of calcium in reperfusion injury is variable and dependent upon a number of metabolic variables.(27) Whether an increase in plasma ionized calcium 30 min after restoration of spontaneous circulation worsens reperfusion injury is uncertain. Calcium overload associated with ischemia and reperfusion is typically manifest as ischemic contracture,(25) a phenomenon not observed in our measurements of left ventricular isovolumetric relaxation (tau) when compared to that measured in untreated animals.

This study has several limitations. We used minimally heparinized standard syringes for blood sampling. Arterial blood sampling devices containing relatively large heparin concentrations may underestimate ionized calcium due to heparin chelation or binding.(28) We used the same sampling method in all animals and, if heparin binding did occur, any error was likely to be systematic. The i-STAT System uses ion-selective electrode potentiometry and measured values are highly correlated ($r = 0.98$) with other methods of measurement.(29) Although we found that a calcium infusion following resuscitation attenuated myocardial dysfunction, only one dose and one infusion rate were used. A different dose or rate of infusion might produce different results. Lastly, we did not evaluate the potential adverse effects of maintaining or raising ionized calcium on cellular pathology or long term postresuscitation outcome.

Calcium therapy for cardiac arrest has a long history.(30–31) Prior to the 1985 standards and guidelines for cardiopulmonary resuscitation and emergency cardiac care, calcium chloride was recommended in the treatment algorithms of asystole and electromechanical dissociation, the latter now called pulse electrical activity (PEA). In 1985, calcium chloride was no longer recommended in these cardiac arrest settings, largely due to the lack of demonstrated benefit and the concern that high levels of calcium following intravenous bolus administration might be detrimental.(14,32,33) The findings of our study suggest that calcium infusion therapy, acting as an inotrope and vasopressor, may be beneficial after resuscitation.

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Figure 1. Mean ionized calcium values both prearrest and following ventricular fibrillation (VF) in pigs. A. Electrically-induced VF (n=65). B. Ischemically-induced VF (n=37). (Error bars represent standard deviations.)

Figure 2. Mean arterial lactate levels both prearrest and following resuscitation from electrically-induced ventricular fibrillation in 26 pigs. (Error bars represent standard deviations.)

Figure 3. Effect of subject-wise deletion of each of 26 animals resuscitated from electrically-induced ventricular fibrillation upon the coefficient for the association between natural-log transformed values of arterial lactate ($\ln[\text{Lactate}]$) and ionized calcium levels. (Range -0.053 to -0.059 , all $p < 0.05$.)

Figure 4. Comparison of mean left ventricular stroke work (LVSW) and mean arterial pressure (MAP) both prearrest and following resuscitation from ventricular fibrillation in pigs assigned to either post-resuscitation infusion of calcium (n=6) or normal saline (control, n=6). (Error bars represent standard deviations.)

Table 1

Control Hemodynamic Variables

	Electrical VF (n = 65)	Ischemic VF (n=37)
Heart Rate (beats/minute)	98 ± 19	104 ± 19
MAP (mm Hg)	91 ± 10	92 ± 11
LVEDP (mm Hg)	5 ± 3	6 ± 3
SV (ml/min)	41 ± 6	42 ± 10
SW (g-m)	47 ± 9	49 ± 13

Table 2

Correlation coefficients between hematologic variables of interest during the early post-resuscitation period following both ischemic ventricular fibrillation (IVF) and electrically-induced ventricular fibrillation (EVF) in pigs (n=65 and 37, respectively).

	Lactate*		Base Excess	pH	
Ionized Calcium	-0.40	(p<0.0001)	EVF 0.34 IVF 0.21	EVF 0.19 IVF 0.10	(p=0.0005) P=0.27
pH	-0.74	(p<0.0001)	EVF 0.84 IVF 0.83		
Base Excess	-0.89	(p<0.0001)			

* Lactate was measured in a subset of 26 EVF animals.

Table 3

Resuscitation variables for control and calcium chloride groups

	CPP (mm Hg)	ETCO ₂ (mmHg)	CS to Defib	Total Joules	Time to ROSC (sec)
Control Group (n=6)	14 ± 3	16 ± 5	1 ± 0.5	467 ± 388	150 ± 77
Calcium Group (n=6)	14 ± 4	17 ± 10	1 ± 0.5	483 ± 508	186 ± 100

Trans thoracic impedance, total shocks administered, number of refrillations, and epinephrine dose were also not different between groups.