The Cardiopulmonary Effects of Calcium Infusion in Infants with Persistent Pulmonary Hypertension of the Newborn

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ABSTRACT. Low blood ionized calcium levels have been reported previously in association with alkalosis in infants undergoing hyperventilation for persistent pulmonary hypertension. We investigated the effect of acute calcium infusions on the cardiopulmonary status of 10 hypocalcemic, hyperventilated infants with persistent pulmonary hypertension. Acid-base status, arterial partial pressure of oxygen, vital signs, and echocardiographically determined right and left systolic time interval ratios and left ventricular shortening fractions were obtained before and after rapid infusions of calcium gluconate or saline. At 5 and 15 min after calcium infusion, but not after saline infusion, there were significant decreases in both right and left ventricular systolic time interval ratios, and an increase in transcutaneous PO_2 and PaO_2 that coincided with peak levels of ionized calcium. These findings provide evidence that high levels of ionized calcium in newborns with persistent pulmonary hypertension transiently improve myocardial performance and oxygenation. (*Pediatr Res* 25:262–265,1989)

Abbreviations

PPHN, persistent pulmonary hypertension of the newborn
TcPO$_2$, transcutaneous PO$_2$

PPHN is a cause of severe hypoxia related to elevated pulmonary vascular resistance and right to left shunting across fetal circulatory channels. The majority of infants with PPHN have a clinical history of perinatal asphyxia (1). Many of these infants also have evidence of myocardial dysfunction. Treatment of PPHN is directed at lowering pulmonary vascular resistance while maintaining systemic blood pressure. Hyperventilation-induced alkalosis is used commonly to lower pulmonary vascular resistance; it is often necessary to raise the pH to ≥ 7.55 to lower pulmonary artery pressures (2). We have shown that this degree of alkalosis substantially lowers blood ionized calcium levels in hyperventilated infants with PPHN (3). Although it has been theorized that low blood ionized calcium may in part mediate the decline in pulmonary vascular resistance with hyperventilation, hypocalcemia may worsen the already impaired myocardial function of infants with pulmonary hypertension (4–7). The present study was designed to assess the effects of ionized calcium infusion on echocardiographically determined cardiac perform-

ance and peripheral oxygenation in hypocalcemic infants with PPHN undergoing treatment with hyperventilation.

MATERIALS AND METHODS

Subjects were selected from infants admitted to the Crouse Irving Memorial Hospital Intensive Care Nursery between December 1984 and February 1986. The diagnosis of PPHN was made in infants of greater than 37 wk of gestational age with severe respiratory distress who met the following criteria:*1*) a PaO_2 of less than 60 torr while breathing 100% oxygen, *2*) an increase in PaO_2 to more than 100 torr during hyperventilation with 100% oxygen, and *3*) the presence of prolonged right and left ventricular systolic time interval rations. No infants selected had hematocrits > 60%, clinical evidence of pulmonary hypoplasia or structural heart disease.

Infants with PPHN were enrolled in the study when they met the following additional criteria: *1*) postnatal age less than 72 h, *2*) need for hyperventilation with an arterial pH ≥ 7.50, *3*) cardiopulmonary stability for at least 2 h with no greater than a 15% fluctuation in oxygenation, pH, or vital signs, *4*) whole blood ionized calcium level ≤ 3 mg/dl and *5*) no previous treatment with tolazoline. Patients were assigned randomly either to receive calcium infusion first, followed 1 h and 10 min later by normal saline, or to receive saline first followed by calcium. Calcium was administered through umbilical arterial catheters as 10% calcium gluconate at a dose of 200 mg/kg over a period of 2 min; normal saline was given similarly and in the same vol (2 ml/kg). Heart rate, blood pressure, ($TcPO_2$), arterial blood gases, and total serum and plasma ionized calcium, and phosphorus were secured 10 min before and 5, 35, and 55 min after each infusion. M-mode echocardiograms were recorded at the same time intervals using a Hoffrel System 202 (Hoffred Instruments, Greenwich, CT) with simultaneous electrocardiogram and a 5 mHz/6 mm nonfocused transducer on light-sensitive paper as previously described (8, 9). Previous studies have documented the accuracy of echocardiographically determined right and left ventricular systolic time intervals (*i.e.* the ratio of the preejection period to ventricular ejection time of the right and left ventricle) and indices of left ventricular performance in both static and changing hemodynamic states (10, 11). Although the right and left systolic time interval ratios are not accurate indices of pulmonary arterial pressure and/or pulmonary vascular resistance, they have been shown to identify infants with PPHN (8). The right and left systolic time interval ratios and shortening fractions of the left ventricle were the means of at least three determinations by one of the authors (R.K.) blinded to study infusion. The velocity of circumferential fiber shortening, an index of myocardial function, was calculated from the ratio of the fiber shortening index to left ventricular ejection time (12). Our normal values in term newborns for these echocardiographic

parameters are: right ventricular systolic time interval, ≤ 0.3; left ventricular systolic time interval, 0.32 – 0.39; shortening fraction of the left ventricle, 0.27–0.39; and velocity of circumferential fiber shortening of the left ventricle, 1.2 ± 0.2 circumferences/s.

Blood for ionized calcium measurements was collected in heparinized syringes without exposure to air and performed in duplicate using a Radiometer flow-through ion electrode (Radiometer America, Inc., Westlake, OH) (3). The normal value for plasma ionized calcium in term infants at 48 h of age is 4.6 ± 0.10 mg/dl with a coefficient of variation of less than 2%. Total serum calcium was determined by EDTA titration (13) and serum phosphorus by a modification of the method of Fiske-Subarow (14).

Echocardiographic, physiologic, and biochemical data at each time period were compared with baseline values before calcium or saline infusion. Data were evaluated by ANOVA using the Method of Fitting Constants followed by Dunnett's t test. All data are presented as the mean ± SEM.

RESULTS

Six males and four females were studies. Their mean gestational age was 39 wk (range 37 – 41 wk) and mean birth wt was 3237 g (range 2120–4460 g). Six infants had the diagnosis of persistent fetal circulation with a clear chest radiograph, three infants had pulmonary hypertension associated with aspiration of meconium or amniotic fluid, and one infant had group B streptococcal sepsis. All babies were paralyzed with pancuronium bromide and hyperventilated with pH between 7.50 and 7.67. All infants received 10–20 μg/kg/min of dopamine to maintain systolic blood pressure > 60 torr. The mean age at the time of study was 38 ± 16 h. Five infants received normal saline first and five infants received calcium first. There were no complications of either infusion.

Table 1 shows the changes in total serum calcium and phosphorus and plasma ionized calcium after infusion of calcium. At 5 min after calcium infusion, total and ionized calcium increased 6.7 ± 0.3 and 3.5 ± 0.3 mg/dl above baseline, respectively ($p <$ 0.01), and both remained significantly elevated for 55 min after infusion ($p < 0.01$). Phosphorus levels were unchanged after calcium infusion. Before saline infusion, baseline values of total calcium, ionized calcium, and phosphorus were 7.1 ± 0.4, 2.9 ± 0.2, and 3.4 ± 0.3 mg/dl, respectively. There were no changes in these values 5, 15, 35, and 55 min after saline infusion (data not shown).

Figure 1 compares the echocardiographic changes with changes in ionized calcium after infusion of calcium and saline. The right and left ventricular systolic time interval ratios are represented as the mean change from preinfusion values. The mean baseline values for right and left ventricular systolic time interval ratios were 0.53 ± 0.07 and 0.55 ± 0.07, respectively. At 5 and 15 min after calcium infusion, there were significant decreases in both systolic time interval ratios that coincided with peak levels of
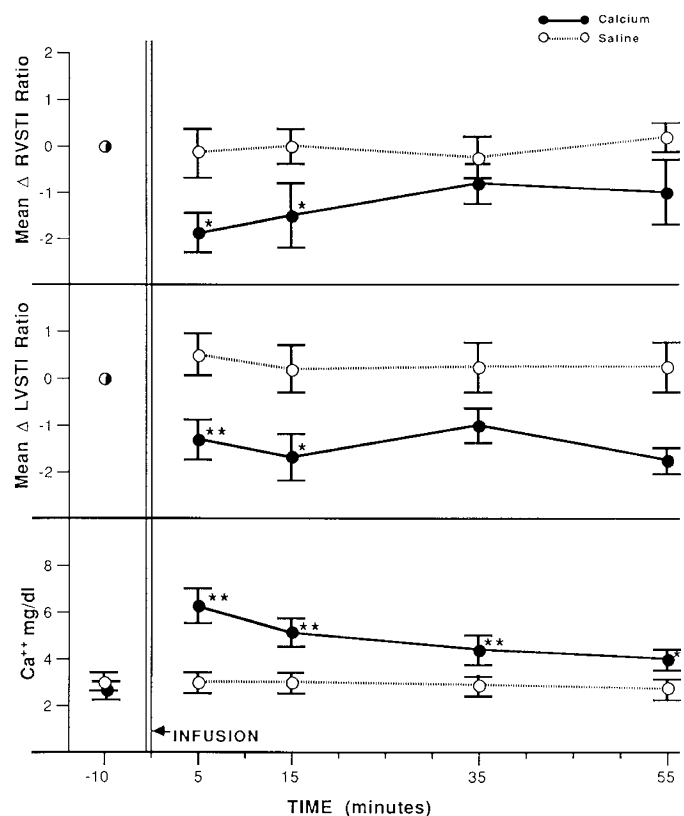
Table 1. *Effect of calcium infusion on total serum calcium, plasma ionized calcium, and serum phosphorus in infants with PPHN**

	Time in relation to calcium infusion (min)				
	−10	5	15	35	55
Total calcium (mg/dl)	7.1	13.8†	11.4†	9.7†	9.2†
	(0.3)	(0.4)	(0.5)	(0.4)	(0.5)
Ionized calcium (mg/dl)	2.6	6.1†	5.1†	4.2†	3.7†
	(0.1)	(0.3)	(0.3)	(0.3)	(0.2)
Phosphorus (mg/dl)	3.4	3.7	3.8	3.8	3.9
	(0.3)	(0.2)	(0.4)	(0.3)	(0.4)

* All values are the mean ± SEM.
† $p < 0.01$ compared to −10 min value.

Fig. 1. Mean change of right ventricular systolic time interval (*upper*) and left ventricular systolic time interval (*middle*) ratios and levels of ionized calcium (*lower*) after Ca gluconate or normal saline. Each point represents the mean ± SEM from −10 min baseline values. * $p < 0.05$; ** $p < 0.01$ from baseline values.

ionized calcium. The decreases in right and left systolic time interval ratios resulted primarily from shortening of the preejection periods. The right ventricular preejection period declined from a baseline mean of 0.074 ± 0.005 s to 0.052 ± 0.003 s at 5 min ($p < 0.01$) and 0.057 ± 0.005 s at 15 min ($p < 0.05$) after calcium infusion. The left ventricular preejection period dropped from a baseline mean of 0.070 ± 0.007 s to 0.054 ± 0.006 s at 5 min ($p < 0.01$) and 0.056 ± 0.007 s at 15 min ($p < 0.05$) after calcium infusion. There were no significant changes in ejection times. Calcium infusion had no effect on the shortening fraction of the left ventricle (0.25 ± 0.08) or the velocity of circumferential fiber shortening (2.2 ± 0.3 circumferences/s). Saline had no effect on any echocardiographic parameter.

Figure 2 compares changes in $TcPO_2$, PaO_2, and ionized calcium levels before and after calcium infusion. The mean baseline value for $TcPO_2$ before calcium and saline infusions was 150 ± 40 mm Hg, and the preinfusion value for PaO_2 was 168 ± 47 mm Hg. Coincident with the rise in ionized calcium and change in cardiac performance was a statistically significant rise in oxygenation. The mean rise in TcO_2 level was 47 torr, 5 min after infusion; this preceded the peak rise in arterial oxygenation of 42 torr, 15 min after calcium infusion. Although, the values remained above baseline, the increase in oxygenation was no longer significantly different 35 and 55 min after infusion.

Calcium and saline infusion had no effect on blood pressure, heart rate, or blood pH.

DISCUSSION

Bolus calcium infusion in hypocalcemic infants with PPHN did not reverse the pulmonary vasodilating effects of alkalosis, but resulted in improved oxygenation and decreased right and left ventricular systolic time interval ratios. These cardiovascular
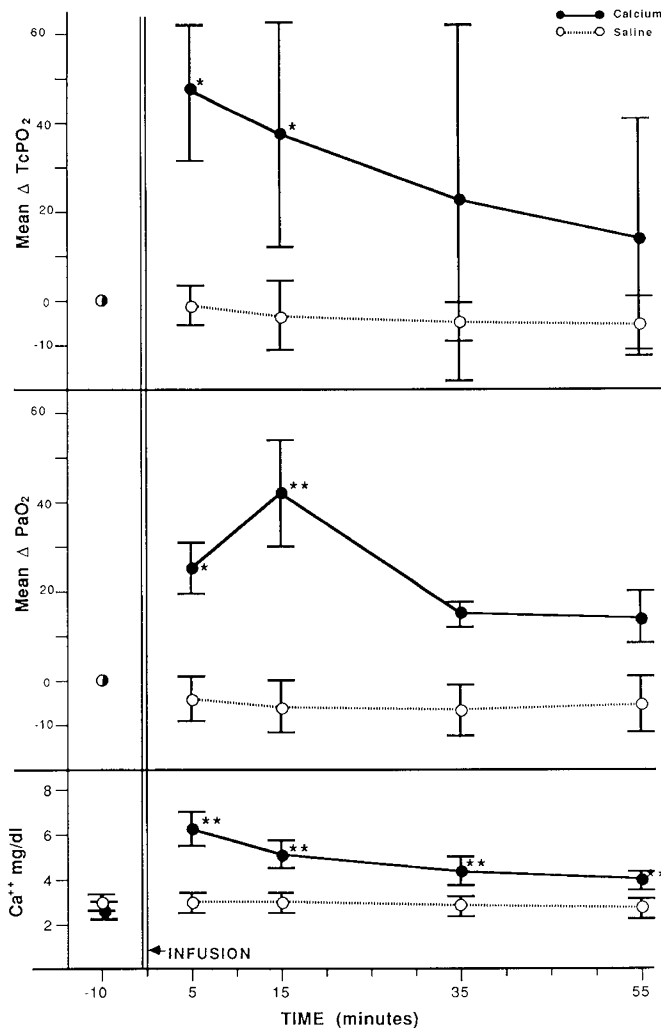
Fig. 2. Mean change in TcPO$_2$ (*upper*), PaO$_2$ (*middle*), and ionized calcium levels (*lower*) after calcium or saline infusions. Each point represents the mean ± SEM from each −10 min value. * $p < 0.05$; ** $p < 0.01$ from baseline values.

effects were not attributable to vol expansion as isovolemic infusions of saline had no effect. These changes could be due to improved myocardial contractility, a decrease in electromechanical delay and/ or a decrease in total vascular resistance (afterload). In the absence of alterations in myocardial contractility, the pressure in the aorta or pulmonary artery determine the systolic time intervals, and a decline in the diastolic pressure in the vessel is reflected in shortening of the preejection period. However, when this principle has been applied to the clinical circumstance of infants with PPHN where there may be impaired contractility, alterations in interval ratios often do not accurately reflect changes in pulmonary artery pressures and/or pulmonary vascular resistance. In normal newborns, the mean velocity of circumferential fiber shortening is a sensitive index of left ventricular function. This measure of ventricular function has not been angiographically validated in infants with PPHN. Although it is not possible to predict echocardiographically the individual contribution of changes in contractility and afterload reduction in infants with PPHN, the fact that calcium infusion reduced the preejection periods of the right and left ventricle with no effect on the shortening fraction or the velocity of circumferential shortening of the left ventricle suggests a vasodilating effect of calcium.

In vitro studies in experimental animals have demonstrated a dual effect of calcium in controlling vascular tone. Whereas

concentrations of calcium in the physiologic range potentiate the contractile response of vascular muscle (15), elevated concentrations of calcium (in the range observed at 5 and 15 min after calcium infusion in this study) diminish the magnitude of contraction of smooth muscle and cause relaxation of already contracted vascular smooth muscle (16).

Drummond (4) hypothesized that the alkalosis-associated decline in pulmonary vascular resistance may, in part, be mediated by a decrease in the concentration of extracellular calcium and/ or an accompanying intracellular sequestration of calcium. This hypothesis is underscored by the fact that smooth muscle, as compared to skeletal muscle, is more susceptible to the extracellular supply of calcium because intracellular stores are of limited capacity and have to be rapidly refilled during mechanical activity (17). However, if increasing the concentration of extracellular calcium had potentiated the contractile response of the pulmonary vascular smooth muscle, we would have expected an increase in right and left preejection periods by echocardiography and a decline in oxygenation associated with an increase in right to left shunting. This is in contrast to our experimental findings on these 10 neonates.

The extent of ionized hypocalcemia in this report is consistent with our previous findings in hyperventilated infants with PPHN (3). Depletion of ionized calcium to this extent has been correlated in previous reports with significant myocardial disturbances in newborns and adults that have been corrected with the administration of calcium (18–20). Mirro and Brown (21), using a study design similar to that of this report, showed that rapid bolus calcium infusions significantly shortened left ventricular preejection periods in preterm infants with hypocalcemia (total serum calcium < 7 mg/dl). Henrich, *et al.* (22) were able to show that the increase in ionized calcium after hemodialysis in adult patients with chronic renal failure was responsible for an improvement in left ventricular contractility. Our group of infants had very low ionized calcium concentrations and evidence of myocardial dysfunction before calcium infusion. Although the primary effect of rapid calcium infusion was to shorten the preejection period with no effect on ejection times and shortening fraction of the left ventricle, an improvement in myocardial performance that resulted in better oxygenation and reduced systolic time interval ratios cannot be excluded.

This study provides evidence that rapid correction of hypocalcemia in newborns with PPHN has no deleterious effect on the alkalosis-mediated decline in pulmonary vascular resistance and transiently improves myocardial performance and oxygenation. Further studies will be directed at attempting to sort out the effects of calcium on contractility and vascular resistance, and the effect of maintaining serum calcium by sustained infusions.

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