Calcium Attenuates Epinephrine’s β-Adrenergic Effects in Postoperative Heart Surgery Patients

Gary P. Zaloga, MD, Robert A. Strickland, MD, John F. Butterworth IV, MD, Lynette J. Mark, MD, Stephen A. Mills, MD, and C. Raymond Lake, MD, PhD

Epinephrine and calcium possess both cardiac inotropic and vasopressor activity. In addition, epinephrine’s cardiovascular effects are mediated via increases in intracellular calcium. As a result, many clinicians administer the two agents together in an attempt to augment their effects. Although this approach seems rational, it has never been proven effective. We evaluated the cardiovascular and hyperglycemic actions of epinephrine (10 and 30 ng/kg/min), with and without calcium chloride administration (10 mg/kg bolus followed by 2 mg/kg/hr infusion), in a prospective, randomized, blinded, crossover designed study. Twelve adult patients were studied 1 day after aortocoronary bypass surgery. Calcium chloride raised ionized calcium levels from 1.06±0.03 (mean±SEM) to 1.44±0.05 mM (p<0.05). Calcium raised mean arterial pressure from 85±1 to 94±2 mm Hg (p<0.05) but had no significant effect on cardiac index. Epinephrine alone at 10 and 30 ng/kg/min significantly raised cardiac index from 2.7±0.2 to 3.0±0.2 (p<0.05) and 3.6±0.3 (p<0.05) l/min/m². After calcium, epinephrine failed to significantly increase cardiac index. Epinephrine at 30 ng/kg/min significantly increased mean arterial pressure from 87±1 to 95±2 mm Hg (p<0.05). After calcium, epinephrine had no significant effect on blood pressure. In addition, epinephrine’s hyperglycemic effect was blunted by calcium. Plasma epinephrine levels were similar during control and calcium infusions. We conclude that calcium blunts epinephrine’s β-adrenergic actions in postoperative cardiac surgery patients. (Circulation 1990;81:196–200)

Epinephrine increases cardiac output via its β-adrenergic inotropic and chronotropic actions. Because of these properties, epinephrine is frequently used to raise blood pressure and improve cardiac output in critically ill patients. Epinephrine’s cardiovascular effects are believed to be mediated through membrane-associated β-adrenergic receptors. These receptors raise free intracellular calcium levels and augment contraction in cardiac tissue and lower free intracellular calcium and depress contraction in vascular smooth muscle.2

Because epinephrine mediates its cardiotonic actions through elevation of free intracellular calcium concentrations, some clinicians administer calcium along with epinephrine in an attempt to augment epinephrine’s effectiveness. Moreover, β-adrenergic inotropic agents are often administered concurrently with calcium immediately after cardiopulmonary bypass.3 Although the coadministration of calcium with epinephrine would seem rational, the effectiveness of this practice in humans has never been documented. We previously demonstrated that calcium administration blunted both glucagon’s chronotropic actions4 and epinephrine’s hypertensive effects5 in animals. This surprising interaction led us to extend our animal study to humans by evaluating the effect of calcium on epinephrine’s cardiovascular and metabolic actions in patients recovering from aortocoronary bypass surgery. These patients are especially appropriate for such studies because they are hemodynamically stable and they retain appropriate monitoring devices needed for studying cardiovascular function. Our findings indicate that calcium administration blunts epinephrine’s cardiac, peripheral vascular, and hyperglycemic (i.e., hepatic) actions.

Methods

After approval of our protocol by our institutional review board, 12 consenting adult patients recovering
from coronary artery bypass surgery were studied on their first postoperative day (i.e., 24 hours after surgery) in the intensive care unit. All patients were extubated and hemodynamically stable; none required inotropic, vasoactive, antihypertensive, or antianginal drug therapy. No patient had received oral (i.e., antianginal) medications for 30 hours before study. All patients had normal renal and hepatic function; none had hypertension or a known disorder of calcium metabolism.

Each patient received both a calcium chloride infusion (mixed with 5% dextrose in water) and a 5% dextrose in water (D5W) infusion in a double-blind, randomized, crossover manner. Six patients received the calcium chloride infusion (10 mg/kg bolus over 5 minutes followed by a 2 mg/kg/hr infusion) first, while the six other patients received a comparable volume of D5W as the initial infusion. After 20 minutes of the calcium or D5W infusion, all patients received two epinephrine infusions (10 ng/kg/min [LEPI] and 30 ng/kg/min [HEPI]), administered incrementally for 8 minutes each. A 15-minute rest period followed in which all infusions were discontinued, allowing all hemodynamic parameters to return to baseline. Then, the experimental sequence was repeated, except that the six patients first given calcium now received D5W, and the six patients first given D5W now received calcium chloride.

Radial artery pressures (systolic, diastolic, mean), central venous pressure (CVP), pulmonary artery pressures (systolic, diastolic, mean), pulmonary capillary wedge pressure (PCWP), heart rate, and duplicate thermodilution cardiac outputs were recorded at baseline, at 10 and 20 minutes into the calcium or D5W infusion and at 4 and 8 minutes of each epinephrine infusion. Cardiac index, systemic vascular resistance index, and pulmonary vascular resistance index were calculated according to standard formulae. Systolic and diastolic arterial pressures, systemic and diastolic pulmonary artery pressures, CVP, heart rate, and ECG lead II were continuously monitored throughout the study but not recorded except at the time points previously described.

Ionized calcium (Nova II, Nova Biomedical, Waltham, Massachusetts), potassium (GEM-STAT, Mallinckrodt Sensor Systems, Ann Arbor, Michigan), and serum glucose (glucose oxidase method) also were measured at each time point. Blood was obtained for measurement of epinephrine and norepinephrine levels in six randomly selected patients at baseline, after the calcium or D5W infusion, and after 8 minutes of each epinephrine infusion. Blood specimens were collected in chilled heparinized test tubes and placed on ice, and the plasma was separated and stored at −70°C until assayed. Plasma epinephrine and norepinephrine concentrations were measured by a radioenzymatic technique in which partially purified catechol-O-methyl-transferase (COMT) catalyzed the transfer of a 3H-methyl group from commercially available 3H-S-adenosylmethionine to the metahydroxyl group of endogenous epinephrine and norepinephrine, forming 3H-metanephrine and 3H-normetanephrine, respectively. This technique accurately measures epinephrine and norepinephrine levels of more than 30–40 pg/mL.

Values are given as mean±SEM. Data were analyzed by repeated-measures analysis of variance followed by Tukey’s multiple comparison test. Maximal epinephrine-induced responses during D5W and calcium chloride infusions were analyzed using paired two-tailed Student’s t tests.

**Results**

Calcium chloride raised ionized calcium levels from 1.06±0.03 to 1.44±0.07 mM (Table 1 and Figure 1). The D5W infusion did not alter ionized calcium levels. After the rest period and D5W infusion (35 minutes), ionized calcium levels returned to within 13% of baseline ionized calcium values in the six patients given the calcium infusion first. Calcium chloride raised mean arterial blood pressure from 85±1 to 94±2 mm Hg but had no significant effect on cardiac index (Table 1 and Figure 1). The D5W infusion did not alter mean arterial blood pressure or cardiac index.

Epinephrine at 10 (LEPI) and 30 (HEPI) ng/kg/min significantly increased cardiac index during the D5W infusion from a baseline of 2.7±0.2 to 3.0±0.2 (LEPI) and 3.6±0.3 l/min/m² (HEPI) (Table 1 and Figure 1). After calcium, epinephrine did not significantly increase cardiac index. The maximal epinephrine-induced increase in cardiac index was depressed by 70% when calcium was administered (Table 1 and Figure 1).

In the absence of calcium, epinephrine (30 ng/kg/min) significantly increased mean arterial blood pressure from 87±1 to 95±2 mm Hg. After calcium, epinephrine did not further elevate blood pressure (Table 1 and Figure 1). Epinephrine had no significant effects on heart rate, pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, or systemic vascular resistance index during either infusion (Table 1).

Epinephrine raised plasma glucose levels during both the D5W and calcium infusions. This hyperglycemic action of epinephrine was blunted during the calcium infusion (Figure 2). Epinephrine had no significant effect on plasma potassium concentrations during either infusion. Plasma epinephrine and norepinephrine levels were similar in both groups at baseline and during each sequential epinephrine infusion (Table 1).

**Discussion**

This study demonstrates that calcium blunts epinephrine’s effects mediated by cardiac β1-receptors (i.e., cardiac index) and hepatic β2-receptors (i.e., hyperglycemia) in patients recovering from aortocoronary bypass surgery. Because calcium and epinephrine both elevate blood pressure and possess cardiac inotropic activity, it has been assumed that coadministration of the two drugs would be synergistic. Our
TABLE 1. Hemodynamic Values and Epinephrine Concentrations

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<th>Infusion</th>
<th>MAP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>HR (beats/min)</th>
<th>PAM (mm Hg)</th>
<th>PCWP (mm Hg)</th>
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* p<0.05 compared with baseline; †p<0.05 compared with B20.

Baseline, baseline; B10, 10 minutes into calcium (C) or dextrose (D) infusion; B20, 20 minutes into C or D infusion; LEPI-4, 4 minutes of 10 ng/kg/min epinephrine; LEPI-8, 8 minutes of 10 ng/kg/min epinephrine; HEPI-4, 4 minutes of 30 ng/kg/min epinephrine; HEPI-8, 8 minutes of 30 ng/kg/min epinephrine; PAM, pulmonary artery mean.

data indicate that calcium may be antagonistic to epinephrine. The diminished effect of epinephrine after calcium administration was not the result of lower circulating epinephrine levels because these were not altered by calcium. Calcium and DSW infusions were administered in either order. Thus, any downregulation of receptors should be similar in each group and cannot explain the reduced epinephrine effect with calcium.

In support of these results, we found in a previous study that calcium attenuated epinephrine’s hypertensive actions in normal rats and that this attenuation was even greater in rats injected with endotoxin. Bohr noted that raising extracellular calcium from 0.2 to 0.3 mM diminished the fast component of epinephrine-induced contraction in rabbit aorta. Both of these results may have involved calcium-epinephrine interaction at α-adrenergic receptors rather than the β-adrenergic effects assessed in the present study.

Other investigators also have noted effects of calcium on other drug actions. Calcium inhibited the constrictor response to norepinephrine in the isolated ear artery of the rabbit,8 the tail artery of the rat,9 and the brachial artery of the dog.10 Baksii11 studied the pressor response to norepinephrine in dietary calcium–deficient rats and vitamin D–supplemented rats. Calcium-depleted rats displayed an augmented pressor response to norepinephrine, whereas hypercalcemic rats had a diminished response. In addition, calcium depresses milrinone-induced inotropy in the left atrium12 and blunts glucagon’s chronotropic actions in rats.4

The exact mechanism by which calcium may attenuate epinephrine’s actions is unknown. Calcium has been reported to depress adenylate cyclase activity in the heart and to stimulate phosphodiesterase activity, thereby reducing cyclic AMP (cAMP) production and increasing its degradation.13,14 Increasing intracellular calcium concentration with calcium or a calcium ionophore depresses cAMP production in isolated human adipocytes stimulated by norepinephrine,15 in fetal adrenal cells stimulated by adrenocorticotropic hormone (ACTH),16 and in rat renal tubules stimulated by vasopressin.17 In addition, we have found that calcium infusion diminishes epinephrine-induced cAMP production in rats.18 Thus, we believe that calcium-induced reduction in epinephrine-stimulated cAMP levels in heart, vascular smooth muscle, and liver are responsible for the effects that we found. Calcium may produce these effects by altering β-adrenergic receptors, interfering with G coupling proteins, depressing the action of adenylyl cyclase, or by augmenting the activity of phosphodiesterases. Further study is needed to determine the exact site of calcium action.

Our data indicate that calcium increases blood pressure but does not augment cardiac index in patients recovering from cardiac surgery. It is possible (but unlikely) that we may have missed a transient increase in cardiac index in the first few minutes after calcium administration that was not maintained 10 minutes later (i.e., at our first postcalcium measurement). One would expect a calcium-induced increase in cardiac index to persist and correlate with circulating ionized calcium levels.

Kugimiya et al19 found increases in cardiac contractility (stroke volume) and aortic blood flow in isolated rat hearts after calcium administration. Stroke
volume was calculated by dividing blood flow by heart rate. However, these hearts were removed from the effects of the nervous system, circulating hormones, and the peripheral vasculature. Moreover, the cardiovascular effects of calcium in intact animals have been variable. Some investigators report no changes in cardiac index or peripheral vascular resistance after calcium administration, whereas others report increases in these variables. Drop et al. found that calcium chloride increased mean arterial blood pressure and systemic vascular resistance in normocalcemic dogs, but that cardiac output and stroke volume remained unchanged. Calcium administration improved mean arterial blood pressure, cardiac output, and stroke volume only in dogs with severe hypocalcemia (ionized calcium, 0.43 mM).

The response of human subjects to calcium has also been variable. Calcium administration has been reported to increase cardiac output in some studies but not others. However, most studies report an increase in blood pressure after calcium administration. In addition, calcium has been reported to improve cardiac contractility using echocardiography when added to the dialysate of renal failure patients. However, these investigators did not measure cardiac output.

It appears that calcium has variable effects on the cardiovascular system in humans. Its actions differ depending on the use of anesthetic agents and other drugs and the presence of hypocalcemia, underlying cardiac disease, and renal failure.

The plasma concentration of glucose is maintained within a narrow range by a complex regulatory system that is based on the counter-balancing effects of multiple hormones (i.e., insulin, glucagon, epinephrine, cortisol). The development of hyperglycemia during epinephrine infusion is a consequence of increased glucose production from the liver and interference with tissue disposal of glucose. Epinephrine-stimulated glucagon secretion (β-adrenergic receptors) also contributes to hepatic glucose production. Finally, epinephrine may inhibit pancreatic β-cell secretion of insulin via α-adrenergic receptors. Calcium may attenuate epinephrine-induced hyperglycemia by diminishing the hepatic β-adrenergic-stimulating effects of epinephrine or by inhibiting epinephrine-induced glucagon secretion. Calcium inhibition of adenylate cyclase may have diminished both epinephrine’s and glucagon’s hepatic actions.

We have found that calcium chloride administration increases mean arterial blood pressure but not cardiac index in patients 1 day after cardiac bypass surgery. In addition, calcium chloride administration causes ionized hypercalcemia and blunts epinephrine’s β-adrenergic actions. We have studied hemodynamically stable patients 1 day after cardiac surgery; the results may not apply to other postoperative or critically ill patients (especially hemodynamically unstable patients). Whether calcium attenuates effects when the drugs are administered immediately after cardiopulmonary bypass also awaits confirmation. Nonetheless, we recommend...
caution when administering epinephrine with calcium and further recommend that cardiac output and blood pressure be monitored closely when infusing these agents into patients.

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References

Key Words · calcium · epinephrine · catecholamines · cardiac output · inotropic agents · surgery, heart
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