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Normal Parathyroid Hormone Responses to Hypocalcemia during Cardiopulmonary Bypass

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To determine whether the calcium–magnesium–parathyroid hormone–calcitriol (vitamin D) axis responds appropriately to the hypocalcemia that routinely follows initiation of cardiopulmonary bypass (CPB), we measured blood ionized calcium (Ca_I), total calcium (Ca_T), total magnesium (Mg_T), ultrafilterable magnesium (Mg_I), total protein, intact parathyroid hormone (PTH), and calcitriol concentrations at eight defined time points in 28 patients undergoing elective cardiac surgery. With the onset of CPB, Ca_I decreased from 1.14 ± 0.02 to 0.91 ± 0.03 mM, $P < 0.05$) (n = 17), and then gradually returned to a normal value by the time of separation from CPB (0.98 ± 0.01 mM). Ca_T, Mg_I, Mg_T, and total protein concentrations declined significantly upon initiation of CPB and remained depressed thereafter. PTH initially decreased upon initiation of CPB (from 50 ± 8 to 24 ± 9 pg/ml, n = 9, $P < 0.05$), remained inappropriately decreased during the early phases of CPB, and then gradually increased to maximal concentrations in response to hypocalcemia (103 ± 15 pg/ml) before emergence. Calcitriol concentrations (n = 8) were unchanged during surgery. Based on these initial results, which suggested an association between hypomagnesemia and the slow PTH response to hypocalcemia, measurements were repeated in 10 additional patients, to whom magnesium (Mg) (1 g $MgSO_4$ in two separate intravenous doses) was administered. Mg administration neither altered the PTH response to ionized hypocalcemia nor hastened the return of Ca_I to normal. We conclude that Mg_T, Mg_I, and Ca_I concentrations remain depressed at the time of separation from CPB, but that routine supplemental administration of neither calcium (Ca) nor Mg is required for the restoration of normal Ca_I values after CPB. (Key words: Hormones: parathyroid hormone. Ions: calcium, magnesium. Surgery, cardiac: cardiopulmonary bypass. Vitamins: calcitriol.)

CALCIUM (Ca) ions regulate numerous cellular activities, including excitation–contraction coupling in smooth and striated muscle.[1] Hypocalcemia decreases cardiac contractility and peripheral vascular resistance. Thus, maintenance of normal or near-normal circulating concentrations of ionized Ca (Ca_I) is important for optimal cardiovascular function after cardiac surgery. Blood Ca_I concentrations are closely maintained within narrow limits by the combined actions of calcitriol and parathyroid hormone (PTH) on bone.[1] For example, a relatively small decrease in Ca_I from 1.26 to 1.19 mM in volunteers rapidly elicited a maximal increase in PTH.[2] The ability of PTH to respond to changes in Ca_I also depends on ionized magnesium (Mg) concentration. Hypomagnesemia blunts the PTH response to ionized hypocalcemia and causes end-organ resistance to PTH and calcitriol.[1]

Ca_I and Mg concentrations have been reported to decrease,[3–10] increase,[11] or not change[12–14] during cardiopulmonary bypass (CPB). Differences in results occurred because in the past, institutions differed in choices of pump priming solutions, some of which contained Ca salts. Currently, there is a more uniform approach to CPB, with the use of crystalloid–colloid priming solutions that lack added Ca. The effect of these solutions on the Ca–Mg–PTH–calcitriol axis has been not been fully evaluated. In addition, the changes in concentrations of ultrafilterable Mg (Mg_I) normally occurring during CPB and the effect produced by alterations in circulating Mg on the integrity of the Ca–Mg–PTH–calcitriol system have not been evaluated. The current study attempts to assess more accurately the integrity of the Ca–Mg–PTH–calcitriol system during CPB by using a new, more specific radioimmunoassay for intact PTH, by measuring Mg_I (which approximates ionized Mg), and by comparing the responses of patients receiving Mg supplementations to those not receiving Mg.

Materials and Methods

All patients gave written informed consent to participate in our study, which was approved by our institutional review board. Twenty-seven patients underwent aortocoronary bypass grafting with hypothermic CPB; 1 patient underwent closure of an atrial septal defect during nor-

TABLE 1. Constituents of Blood Cardioplegia Solution

Cardioplegic Additive	Induction	Maintenance
CPD (mM)	0.8–1.0	0.8–1.0
Glutamate (mM)	13	13
Aspartate (mM)	13	13
KCl (mM)	27	—
Lidocaine (mM)	0.20	0.28

THAM (tromethamine solution, 0.3 M) was added to obtain a final *p*H of 7.7–7.8.[15]

Induction = solution used to induce arrest; maintenance = solution used for maintenance of arrest; CPD = citrate–phosphate–dextrose solution measured as millimolar concentration of citrate; KCl = potassium chloride.

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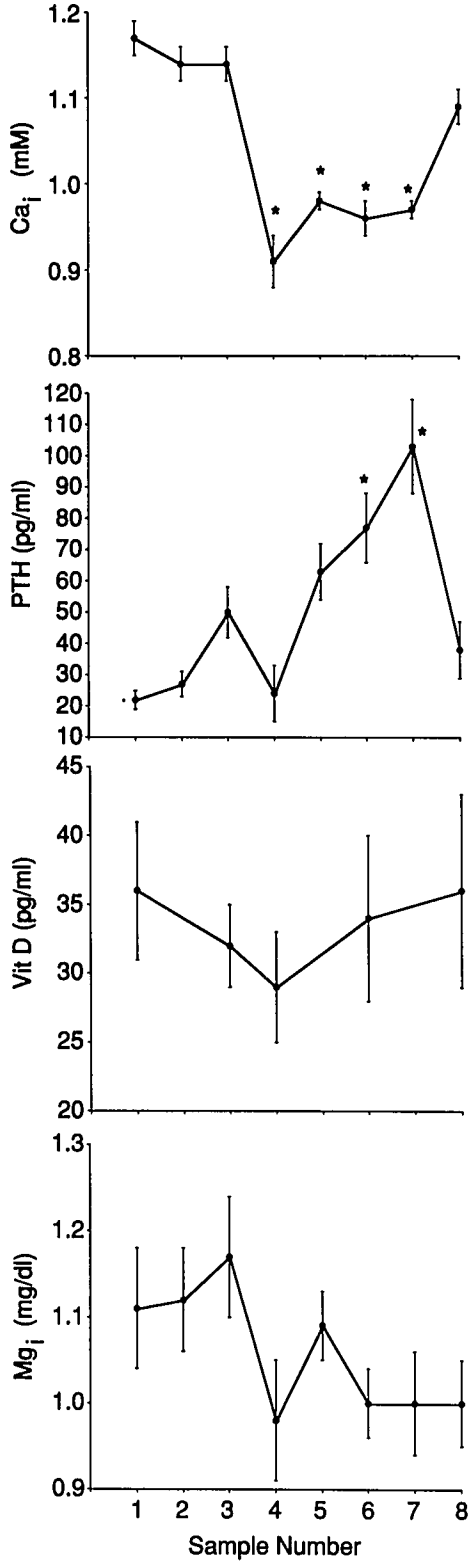

FIG. 1. Ionized calcium (Ca_I) (n = 17), parathyroid hormone (PTH) (n = 9), calcitriol (vit D) (n = 8), and ultrafilterable magnesium (Mg_I) (n = 8) concentrations before (samples 1–3), during (samples 4–7), and after (sample 8) CPB. Data are displayed as means ± SEM. Large decreases in the concentrations of all four blood components occurred upon initiation of bypass perfusion (sample 4). Increased PTH concentrations later on during bypass (samples 5–7) restored Ca_I to normal after bypass (sample 8), whereas Mg_I remained depressed. Calcitriol concentrations were not altered by CPB. The timing of sample collection is described in detail in Materials and Methods. *$P < 0.05$ relative to baseline, preinduction values (sample 1).

mothermic CPB. Patients were excluded if they had valvular heart disease or an abnormality of Ca metabolism. All patients received oral lorazepam (50 μg/kg) and intramuscular morphine (0.08 mg/kg) as preanesthetic medication. An intravenous anesthetic consisting of fentanyl (50–75 μg/kg), pancuronium (0.15–0.25 mg/kg), midazolam (0.15–0.45 mg/kg), and in some cases, metocurine (0.1–0.3 mg/kg) and lorazepam (1–2 mg), was used. Eight arterial blood samples were collected anaerobically from each patient before, during, and after cardiac surgery. Samples were collected at the following intervals: 1) before induction of anesthesia; 2) after induction of anesthesia; 3) 3 min after anticoagulation with heparin; 4) 2 min after initiation of CPB; 5) 5 min after administration of the cardioplegic solution into the cross-clamped aortic root; 6) early during rewarming, at a blood temperature of 30° C; 7) late during rewarming, at a rectal temperature of 35° C; and 8) after placement of the sternal wires.

CPB was performed with a membrane oxygenator primed with 1,250 ml lactated Ringer's solution, 250 ml 5% albumin, 50 ml sodium bicarbonate (44 mEq), 100 ml mannitol (25 g), and 10 ml heparin sulfate (10,000 U). The compositions of our cardioplegic solutions are listed in table 1.[15] Tromethamine 0.3 M was added in sufficient amounts to maintain *p*H at 7.7–7.8. Dextrose solution (5%) was added to maintain osmolality at 320–360 mOsm. Blood cardioplegia was made by mixing these components in a 1:4 volume:volume ratio with blood. The mean ischemic time was 60 min (range 17–126 min), and the mean total CPB time was 129 min (range 44–242 min). Arterial *p*H was maintained at 7.40 ± 0.05 during bypass using the α-stat method (uncorrected for temperature).

We divided our patients into two groups. In the first group (17 patients), no intravenous $MgSO_4$ was given, and we measured Ca_I, total calcium (Ca_T) (n = 17), total magnesium (Mg_T) (n = 17), intact PTH (n = 9), calcitriol (n = 9), and Mg_I (n = 8). The second group (10 patients) received intravenous $MgSO_4$ 1 g prior to CPB and 1 g after 30 min of CPB so that we could assess the effect of Mg repletion on the function of the Ca–Mg–PTH–calcitriol system. We measured Ca_I, Mg_T, and intact PTH in these 10 patients. Data from 1 additional patient, perfused at normothermia for atrial septal defect repair without $MgSO_4$ supplementation, are reported separately.

Anaerobic blood samples were analyzed for Ca_I on a Nova-II instrument (Nova Biomedical, Waltham, MA).

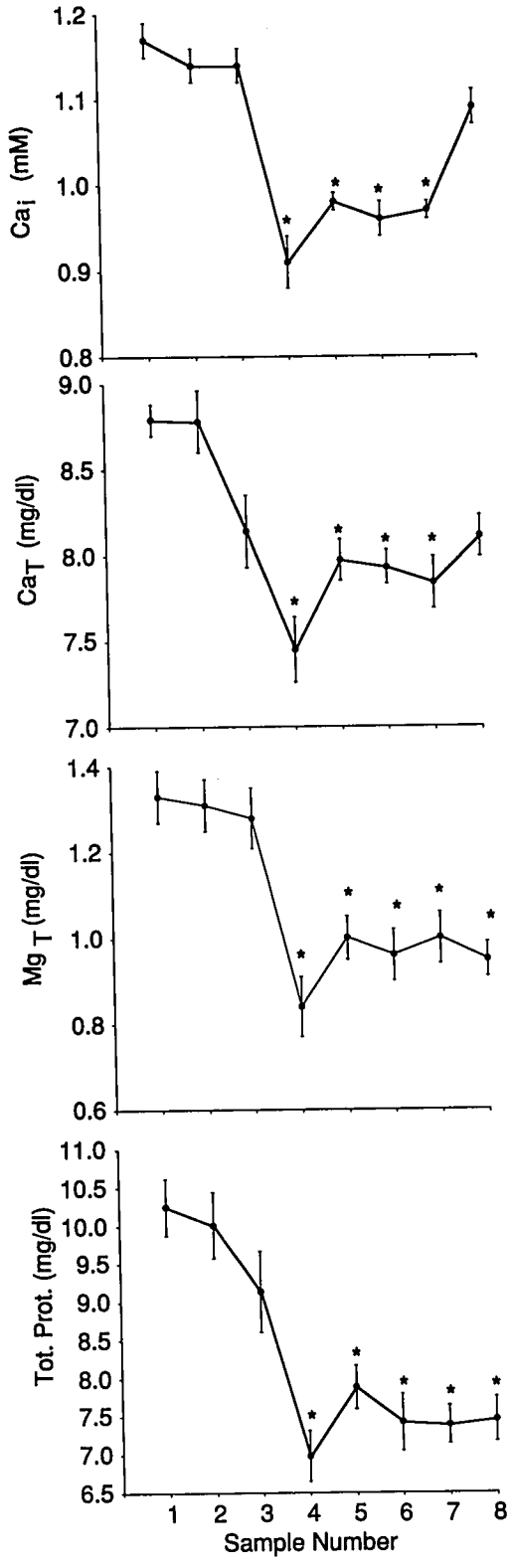

FIG. 2. Ionized calcium (Ca_I) (n = 17), total calcium (Ca_T) (n = 9), total magnesium (Mg_T) (n = 9), and total protein (Tot. Prot.) (n = 9) concentrations before (samples 1–3), during (samples 4–7), and after (sample 8) CPB. Large decreases in all four blood components occurred upon initiation of CPB (sample 4). Increased concentrations of PTH (see fig. 1) restored Ca_I to normal following bypass; however, Ca_T, Mg_T, and total protein remained depressed during and after bypass. *$P < 0.05$ relative to baseline, preinduction values (sample 1).

Arterial *p*H was determined using a blood gas analyzer (Instrumentation Laboratory, Lexington, MA). For Mg_I determination, an aliquot of blood was filtered immediately through Amicon filters (Amicon, Bedford, MA) and the ultrafiltrate frozen for subsequent colorimetric assay.[16] After determination of Ca_I, all samples were centrifuged, and the plasma was separated and frozen for subsequent batch analyses. Total protein was determined using the Bradford protein assay (Bio-Rad, Oakland, CA).[17] Ca_T and Mg concentrations (in the patients to whom no $MgSO_4$ was given) were determined using colorimetric assays (Sigma, St. Louis, MO). Mg concentrations in the patients to whom supplemental $MgSO_4$ was given were determined using a colorimetric assay manufactured by Kodak (Rochester, NY). Thus, baseline Mg concentrations differ slightly between control patients and those to whom $MgSO_4$ supplementation was given. Plasma intact PTH was measured using the Allegro (Incstar, Stillwater, MN) radioimmunoassay. Calcitriol was analyzed by radioimmunoassay (Incstar, Stillwater, MN). Results are expressed as the mean ± standard error of the mean. Statistical significance at $P < 0.05$ was determined by Scheffé's test after one- and two-factor analysis of variance (ANOVA) for repeated measures.

Results

GROUP 1: NO $MgSO_4$

Concentrations of Ca_I, PTH, calcitriol, and Mg_I are shown in figure 1. Ca_I concentrations gradually declined prior to CPB. With the initiation of CPB, Ca_I decreased significantly (from 1.14 ± 0.02 to 0.91 ± 0.03 mM, $P < 0.05$, n = 17), most likely due to hemodilution by the relatively hypocalcemic CPB priming solutions (priming solution Ca_I = 0.81 ± 0.04 mM, n = 12). Near the end of CPB (sample 7), Ca_I returned to near-normal values (0.97 ± 0.01 mM, n = 17); by the time sternal wires were placed (sample 8), Ca_I had returned to normal (1.09 ± 0.02 mM, n = 17).

In the prebypass period, PTH increased appropriately in response to small decreases in Ca_I (fig. 1). In response to this small decline in Ca_I, PTH doubled (27 ± 4 to 50 ± 8 pg/ml, n = 9). With the initiation of CPB, hemodilution resulted in a significant decrease in the highly water-soluble PTH to 24 ± 9 pg/ml (n = 9). Thereafter, PTH concentrations increased rapidly, to 62 ± 9 pg/ml (sample 5), in response to the decline in Ca_I. Between samples 4 and 5 (approximately 20 min), PTH more than doubled. Although PTH achieved 60% of its maximum response

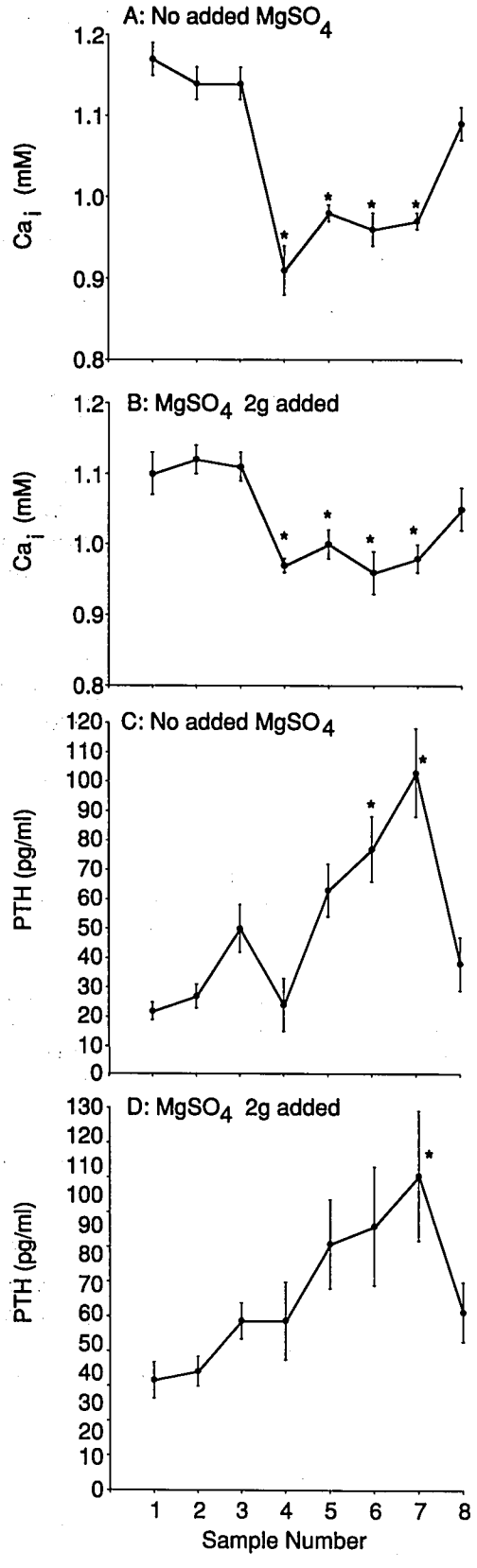

FIG. 3. Ionized calcium (Ca_I) (*A,B*) and parathyroid hormone concentrations (PTH) (*C,D*) before (samples 1–3), during (samples 4–7), and after (sample 8) CPB in control (no added $MgSO_4$) patients (*A*, n = 17; *C*, n = 9) and in patients receiving $MgSO_4$ 2 g iv (*B*, n = 10; *D*, n = 10). Addition of $MgSO_4$ prevented the decrease in total magnesium concentration during and after CPB (data not shown) but had no effect on Ca_I and PTH. *$P < 0.05$ relative to baseline, preinduction values (sample 1).

at sample 5, only after an additional 90 min did the PTH achieve its maximum concentration (103 ± 15 pg/ml).

Concentrations of calcitriol (a hydrophobic molecule with a large volume of distribution) did not change significantly at any point during the study (fig. 1). Mg_I concentrations demonstrated a significant decline during our study (by ANOVA), but these concentrations did not differ significantly from baseline at any specific sample time. In contrast to Ca_I, Mg_I values did not return to normal during or after CPB.

Ca_T, Mg_T, and total protein concentrations demonstrated pronounced, statistically significant decreases upon initiation of CPB (fig. 2). Unlike Ca_I, these components did not return to normal concentrations after CPB (fig. 2).

The single patient who underwent closure of an atrial septal defect was maintained at near normal body temperatures (> 35° C) throughout CPB. The changes in Ca_I and PTH in this patient were similar to those of the hypothermic patients described above.

GROUP 2: $MgSO_4$

To determine whether the sustained decrease in Mg_T measured during CPB in group 1 patients impaired PTH release and possibly delayed the return of Ca_I to normal concentrations, we measured Ca_I and PTH concentrations in 10 additional patients who received a total of 2 g $MgSO_4$ (16 mEq) during CPB. One gram $MgSO_4$ was given immediately prior to initiation of CPB; an additional 1 g $MgSO_4$ was administered 30 min later. With the use of this $MgSO_4$ dosing regimen, Mg_T concentrations in these patients were maintained near control values during CPB (see table 2). Figure 3 compares the Ca_I and PTH responses of patients receiving additional $MgSO_4$ with those of patients not receiving $MgSO_4$. No significant differences between the two groups could be demonstrated at any time point.

Discussion

Our data suggest that the Ca–Mg–PTH–calcitriol system functions adequately during hypothermic CPB. Concentrations of Ca_I, the regulated component, returned to normal as a consequence of PTH release and action upon bone. Ca_T, an indirect measure of Ca_I, remained depressed. Mg_I, Mg_T, and total protein, none of which is regulated by hormonal control systems, remained de-

TABLE 2. Comparison of Total Magnesium Concentrations in Control Patients and Those Receiving $MgSO_4$

	Sample Number							
	1	2	3	4	5	6	7	8
No $MgSO_4$ (n = 17)	100	98 ± 5	96 ± 5	63 ± 5*	75 ± 4*	72 ± 5*	76 ± 5*	71 ± 3*
$MgSO_4$ added (n = 10)	100	96 ± 2	88 ± 4	82 ± 5	125 ± 8	109 ± 6	117 ± 9	101 ± 6

Magnesium concentrations (milligrams per deciliter) are expressed as percentages of the sample 1 value.

* $P < 0.05$ by Scheffé's F test compared to baseline, preinduction value (sample 1). The timing of blood samples is given in the text.

pressed during and after CPB. Finally, concentrations of calcitriol neither decreased upon initiation of CPB nor changed significantly thereafter.

Previous studies of Ca homeostasis during CPB have yielded conflicting results, primarily due to differences in pump priming solutions and in sampling techniques and times.[3–14] Thus, despite these many studies, the degree of functional integrity of the Ca–Mg–PTH–calcitriol system in patients undergoing cardiac surgery remained poorly documented. Moreover, prior measurements of PTH during cardiac surgery used assays sensitive to both active PTH and inactive PTH breakdown products. Finally, no previous report measured Mg_I (which approximates ionized Mg, the active Mg species) during CPB. Since Ca salts are often administered at the termination of CPB, we designed this study to determine whether the Ca–Mg–PTH–calcitriol system was sufficiently impaired during and after CPB to justify this practice.

In agreement with others,[3–10] we found that Ca_I decreased upon initiation of CPB. However, in contrast with some previous studies[3–5,7–10] and in agreement with another,[6] at the end of bypass our patients were only mildly hypocalcemic. By the time of chest closure, Ca_I had returned to normal. Few previous studies have determined Ca_I during CPB conducted with a blood-free priming solution (to which no Ca has been added), which is the current standard of practice.

PTH concentrations began to increase before CPB was established. Although a potential mechanism is the effect of heparin to reduce Ca_I concentration, no significant difference could be demonstrated between Ca_I concentrations at samples 2 and 3. Thereafter, continuing hypocalcemia ultimately elicits maximal PTH secretion. Conlin *et al.*[2] found comparable peak PTH responses to hypocalcemia, in postmenopausal women with osteoporosis; however, the rate of increase in PTH in these women was greater than in our patients during hypothermic CPB. In agreement with our study, Gray *et al.*[6] demonstrated a decrease in PTH concentrations upon initiation of CPB; however, in that study, PTH levels returned to normal and did not increase to maximal levels during CPB.

Mg is known to alter both the secretion of PTH and the end-organ response to PTH.[1] Thus, we sought to determine whether the mild hypomagnesemia measured during CPB altered either PTH secretion or end-organ responses to PTH. However, in the 10 patients given 2 g $MgSO_4$, maintenance of normal to high Mg_T concentrations affected neither the PTH response nor the concentration of Ca_I. We suspect that mild systemic hypomagnesemia (such as that measured in our control patients [group 1]) is much less important in regulating the PTH response to hypocalcemia than is intracellular hypomagnesemia.

It is possible that hypothermia may decrease synthesis and/or release of PTH. Although we cannot completely exclude hypothermia as the cause of continuing hypocalcemia during CPB, our single normothermic patient showed changes in Ca_I and PTH identical to our hypothermic ones, making hypothermia a less attractive explanation. It is possible that components of the cardioplegic solution may inhibit PTH synthesis or release. Nonpulsatile flow on CPB may also affect the release of PTH; however, coincident with rewarming and reperfusion, PTH concentrations increased to maximal values.

Our data suggest three conclusions. First, the Ca–Mg–PTH–calcitriol system functions normally during CPB, despite nonpulsatile perfusion and profound hypothermia. Second, given that concentrations of Ca_I spontaneously return to normal during and after bypass, there appears to be little need for routine administration of Ca salts if one's goal is to restore Ca_I to normal. Third, 2 g intravenous $MgSO_4$ maintains Mg_T concentrations at normal values during and after CPB. We have recently shown that $CaCl_2$ supplementation in patients emerging from CPB[18,19] does not increase myocardial performance. High doses of Ca inhibit the responses of cardiac surgery patients to low-dose epinephrine infusions.[20] Current evidence suggests that elevated Ca_I may be deleterious in the setting of acute ischemia.[21] Thus, we do not recommend routine administration of Ca salts to patients emerging from CPB.

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