

Comprehensive analysis of citrate effects during plateletpheresis in normal donors

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BACKGROUND: Although plateletpheresis procedures are generally well tolerated, the clinical and metabolic consequences associated with rapid infusion of up to 10 g of citrate are underappreciated, and a comprehensive description of these events is not available.

STUDY DESIGN AND METHODS: Clinical and laboratory changes were studied in seven healthy donors undergoing three 90-minute plateletpheresis procedures each, at continuous, fixed citrate infusion rates of 1.1, 1.4, and 1.6 mg per kg per minute.

RESULTS: Serum citrate levels increased markedly with increasing citrate infusion rates and did not achieve a stable plateau. As citrate infusion rates increased, the total volume processed and platelet yields also increased, but donor symptoms became more severe. Ionized calcium (iCa) and ionized magnesium (iMg) concentrations decreased markedly, by 33 and 39 percent below baseline, respectively, at a citrate rate of 1.6 mg per kg per minute. Intact parathyroid hormone levels were higher at 30 minutes than at later time points, despite progressive decreases in iCa and iMg. Urine citrate, calcium, magnesium, sodium, and potassium concentrations and urine pH values increased markedly during all procedures.

CONCLUSION: Marked, progressive increases in serum citrate levels occur during plateletpheresis, accompanied by symptomatic decreases in iCa and iMg, with significantly increased renal excretion of calcium, magnesium, and citrate.

Citrate has been used for more than half a century to anticoagulate stored blood,¹ and it has been the anticoagulant of choice in plateletpheresis procedures for more than two decades.² During the course of a standard plateletpheresis procedure, a donor may receive up to 10 g (53 mmol) of citrate over 90 to 120 minutes.³ Citrate-related effects due to decreased levels of ionized calcium (iCa) occur commonly in apheresis, and they are considered physiologic and of little consequence.⁴ Although earlier studies have documented changes in iCa, parathyroid hormone (PTH), and ionized magnesium (iMg) with increasing serum citrate levels, the time course and magnitude of these changes as a function of the citrate infusion rate have not been fully studied over commonly utilized ranges.^{2,5-11} Furthermore, although previous investigators have advocated a more complete analysis of the renal changes associated with citrate anticoagulant infusion,¹² the excretion of calcium and magnesium during plateletpheresis has not previously been studied. A more complete understanding of these effects would be beneficial, as citrate-related

ABBREVIATIONS: CIR(s) = citrate infusion rate(s); iCa = ionized calcium; iMg = ionized magnesium; iPTH = intact PTH; Pi = inorganic phosphorus; PTH = parathyroid hormone; WB:AC = whole blood to anticoagulant; WBFR(s) = whole-blood flow rate(s).

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symptoms remain an important limitation to procedure flow rates and thus to component yields. To more fully characterize citrate responses, we performed a pilot study in normal donors undergoing standard plateletpheresis procedures at three different, commonly used citrate infusion rates.

MATERIALS AND METHODS

Donors

Study subjects were healthy volunteer platelet donors chosen to provide a representative distribution of sex and weight. Donors met AABB eligibility criteria for plateletpheresis donation and gave informed consent for participation in the study. Subjects were required to have bilateral peripheral venous access and normal liver and renal function tests. Donor blood volumes were calculated by sex, height, and weight as described previously.²

Plateletpheresis procedures

Procedures were performed with the use of a continuous-flow blood cell separator (CS-3000 Plus, Baxter Healthcare, Deerfield, IL) using ACD-A (Baxter) containing 21.3 mg per mL of citrate as trisodium citrate and citric acid.³ Donors underwent three procedures each, during which constant citrate infusion rates of 1.1, 1.4, and 1.6 mg per kg per minute were used, with at least 4 weeks between successive procedures. The first plateletpheresis procedure was performed to define the metabolic changes associated with a citrate infusion rate of 1.6 mg per kg per minute. Because of the unexpectedly profound changes observed, two additional procedures were performed, at 1.1 and 1.4 mg per kg per minute, in random order, to more clearly define the dose relationship between citrate and its metabolic effects. Whole-blood flow rates (WBFRs) and ratios of whole blood to anticoagulant (WB:AC) were maintained throughout each plateletpheresis procedure at values determined in advance to achieve constant citrate infusion rates of 1.1, 1.4, and 1.6 mg per kg per minute. These rates were chosen to span the rates commonly encountered in plateletpheresis while remaining within the bounds recommended by the apheresis device manufacturer. As an example, a WBFR of 50 mL per minute and a WB:AC ratio of 10:1 deliver 1.6 mg per kg per minute of citrate to a representative 60-kg donor and 1.1 mg per kg per minute to a 90-kg donor. All procedures were terminated at 90 minutes.

Laboratory analysis

Blood samples for laboratory analysis were obtained from a sterile port placed on the apheresis withdrawal line 5 inches from the anticoagulant port. Samples were obtained at 0 (baseline), 30, 60, and 90 minutes into the procedure. Samples were collected anaerobically and sent immediately for analysis of serum iCa, iMg, and pH with the use of an electrolyte analyzer (AVL 988-4, AVL Scientific, Roswell, GA). Serum and

urine citrate levels were measured enzymatically with an analyzer (COBAS FARA, Roche Diagnostics Systems, Montclair, NJ) by use of a commercial kit (Boehringer Mannheim, Mannheim, Germany). The imprecision of the method for measurement of citrate (mean; CV%) was 1.04 mmol per L; 1.77 percent and 2.13 mmol per L; 1.09 percent, respectively. Another analyzer (Hitachi 917, Roche Diagnostics, Indianapolis, IN) was used to analyze total calcium, total magnesium, and other electrolytes. Citrate at 5 mmol per L did not interfere with measurements of these values. Plasma samples for intact PTH (iPTH) were analyzed by using a chemoluminescence immunoassay (IMMULITE, Diagnostics Products Corp., Los Angeles, CA). The imprecision of the iPTH method (mean; CV%) was 63 ng per L; 4.3 percent and 447 ng per L; 6.4 percent. Urine electrolytes and creatinine were determined with the use of a clinical system (Synchron CX9 ALX, Beckman Coulter, Brea, CA). Serum and urine phosphorus were measured as inorganic phosphorus (Pi) in mg per dL. Other electrolytes were measured in mmol per L. Urine samples were obtained immediately before (baseline) and after plateletpheresis. Urine electrolyte excretion was estimated by calculating the ratio of urine electrolyte and urine creatinine.

Donor symptom assessment and management

Donor symptoms such as paresthesias, cramping, nausea, and other complaints were assessed by experienced apheresis nurses as "0" if none, "1" if barely noticeable, "2" if irritating, "3" if uncomfortable, and "4" if unbearable. For symptoms that were ≥ 2 , the citrate infusion rate was reduced 16 percent by decreasing the whole blood processing rate by a corresponding amount. The procedure was interrupted for symptoms that were ≥ 3 .

Statistical analyses

Graphics and statistical comparisons were performed with a statistical application (Excel, Microsoft, Redmond, WA). Comparisons of results obtained at different citrate infusion rates for subjects undergoing otherwise identical procedures were made by using a two-tailed, paired *t* test. Percentage changes in the concentrations of serum and urine analytes were calculated by using 100 percent as the baseline concentration. The iCa and iMg fractions were calculated as follows:

$$FiCa = [iCa] / [tCa]$$

and

$$FiMg = [iMg] / [tMg],$$

where FiCa = the fraction of iCa, and FiMg = the fraction of iMg.

RESULTS

Donor demographics and responses

Four men and four women consented to participate in the study. One woman withdrew because of inconvenience, af-

ter one donation at a citrate infusion rate (CIR) of 1.6 mg per kg per minute, during which she experienced Level 3 symptoms. The demographics, volume processed, and component yields for the seven donors completing the study are shown in Table 1. Subjects were experienced plateletpheresis donors, with a mean of 62 (median, 46; range, 3-247) prior donations. The mean initial whole-blood processing rates were 57 mL per minute at a CIR of 1.6 mg per kg per minute, 54 mL per minute at 1.4 mg per kg per minute, and 47 mL per minute at 1.1 mg per kg per minute. The volume processed over 90 minutes increased significantly with higher CIRs, as they resulted in higher WBFRs. Similarly, the platelet yield increased significantly at CIRs of 1.4 and 1.6 mg per kg per minute, as compared to the yield at 1.1 mg per kg per minute ($p < 0.002$). The mean (range) infusion rate of anticoagulant, expressed as milliliters of ACD-A per liter of estimated donor blood volume per minute at each weight-based CIR, was 0.82 (0.72-0.91) at 1.1, 1.05 (0.96-1.16) at 1.4, and 1.15 (1.06-1.21) at 1.6 mg per kg per minute.

There was a trend toward more severe citrate-related symptoms at the highest CIR (Table 2). Two donors experienced citrate-related symptom scores of 3 at a CIR of 1.6 mg per kg per minute, one had a symptom score of 3 at 1.4 mg per kg per minute, and no donors had scores of 3 at 1.1 mg per kg per minute. Similarly, three donors were asymptomatic at a CIR of 1.1, while none was asymptomatic at 1.4 mg per kg per minute, and only one was asymptomatic at 1.6 mg per kg per minute.

Changes in laboratory values

The levels of iCa and iMg fell progressively without reaching a plateau (Fig. 1A). Levels were significantly lower at each 30-minute interval than at the prior interval, so that nadirs universally occurred at 90 minutes (Table 3). Mean nadirs, in mmol per L (% change from baseline), were 0.95 (-23%) at 1.1, 0.86 (-30%) at 1.4, and 0.80 (-33%) at 1.6 mg per kg per minute for iCa and 0.43 (-26%) at 1.1, 0.35 (-37%) at 1.4, and 0.32 (-39%) at 1.6 mg per kg per minute for iMg. Mean iCa and iMg nadirs were significantly lower with each incremental increase in the CIR (Table 3).

Serum citrate levels increased continuously during plateletpheresis, without reaching a plateau. Higher CIRs were associated with significantly higher serum citrate levels at every interval at which they were measured (Fig. 1B), with peak citrate concentrations achieved at 90 minutes (Fig. 2). Serum iCa, iMg, FiCa, and FiMg showed a strong negative correlation with increasing serum citrate levels (Fig. 2). In contrast, iPTH levels were highest at 30 minutes, despite continued declines in iCa levels at 60 and 90 minutes (Fig. 3).

TABLE 1. Donor demographics and product yields

Donor number	Sex	Age	Weight (kg)	Prior donations	Volume processed (L)			Platelet yield ($\times 10^{11}$ cells)		
					1.1 CIR*	1.4 CIR	1.6 CIR	1.1 CIR	1.4 CIR	1.6 CIR
1	M	66	85	82	4.4	5.7	5.7	4.6	4.9	4.6
2	M	54	76	247	3.9	4.7	5.5	4.6	4.9	5.4
3	M	44	75	46	4.1	4.8	5.7	2.8	3.5	4.5
4	F	54	66	18	3.6	4.3	4.8	3.4	3.9	4.1
5	M	42	70	3	3.8	4.6	5.2	3.6	5.6	6.5
6	F	62	61	11	3.3	4.0	4.8	3.5	4.6	5.1
7	F	51	63	24	3.3	4.1	4.8	3.3	4.5	5.1
Mean		53	71	62	3.8	4.6	5.3	3.7	4.6	5.0

* CIR = mg per kg per minute.

TABLE 2. Donor symptom scores during plateletpheresis

CIR (mg/kg/min)	Mean WBFR (mL/min)	Maximum symptom score*			
		0	1	2	3
1.1	47	3/7	2/7	2/7	0/7
1.4	54	0/7	4/7	2/7	1/7
1.6	59	1/7	4/7	0/7	2/7

* Symptom scores were "0" = none, "1" = barely noticeable, "2" = irritating, "3" = uncomfortable.

Additional changes in serum laboratory results that were observed at the completion of plateletpheresis are shown in Fig. 4. Mean serum phosphorus levels decreased by 31 percent. Significant, but more modest, changes were also observed in serum total calcium (3% decrease), sodium (1% increase), potassium (6% decrease), and bicarbonate (3% increase). Mean serum pH increased from 7.40 to 7.42. No significant change was observed in total serum magnesium (1% decrease; $p = 0.42$). At the completion of plateletpheresis, the mean values for these analytes remained within the normal reference range, except for the phosphorus concentration (mean, 2.0 mg/dL; reference range, 2.3-4.3 mg/dL). There was no clear association between changes in the serum concentration of these analytes and changes in serum citrate concentration or CIRs.

The effect of the administration of citrate anticoagulant preservative solution on changes in the concentrations of urine analytes is shown in Fig. 5. The calculated analyte:creatinine ratios for citrate, calcium, and magnesium were markedly greater in urine samples collected immediately after plateletpheresis than in those collected just before plateletpheresis. The mean ratio for citrate increased by 2200 percent, that for total calcium by 310 percent, that for magnesium by 90 percent, that for sodium by 200 percent, and that for potassium by 260 percent. The mean urine pH also increased from 5.6 before plateletpheresis to 7.6 immediately after plateletpheresis, which corresponded to a 99-percent decrease in urinary hydrogen ion concentration. The effect of an increased urine citrate concentration on urine molar ratios (cation:citrate [both mmol/L]) for calcium, magnesium, sodium, and potassium is shown in Table 4.

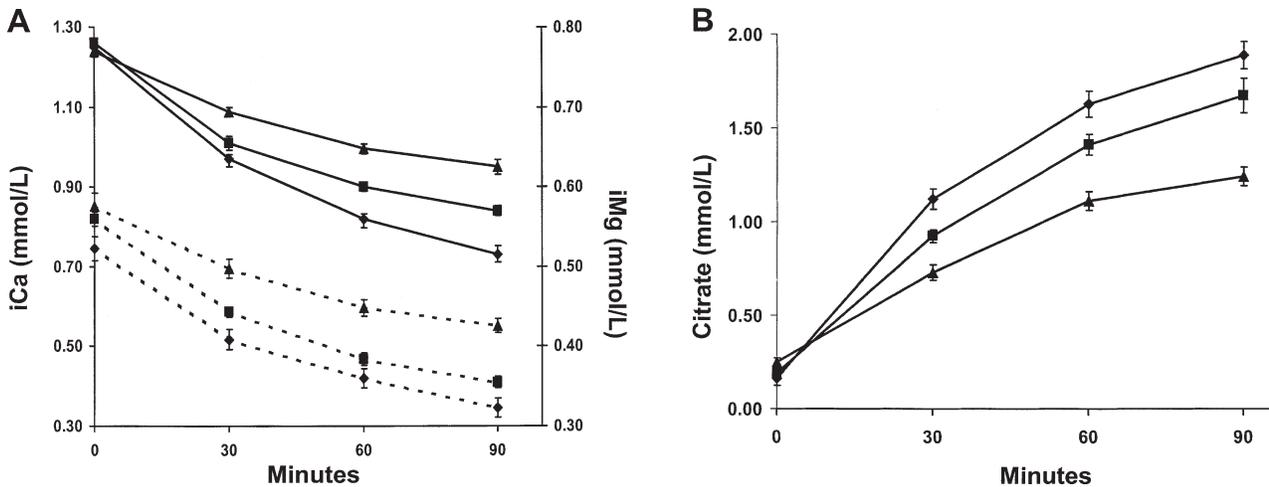


Fig. 1. Changes in serum concentrations of divalent cations (A) and citrate (B) during plateletpheresis. Procedures at 1.6 mg per kg per minute, ◆; those at 1.4 mg per kg per minute, ■; and those at 1.1 mg per kg per minute, ▲. Levels of both iCa (—) and iMg (---) fell continuously over the 90-minute procedures, without reaching a stable plateau, and the largest decreases were observed at the highest CIR. Similarly, serum citrate levels increased continuously, without reaching a plateau, with the largest increases at the highest CIR. Error bars are the standard error of the mean.

TABLE 3. Lowest laboratory values during plateletpheresis

Donor number	iCa (1.17 - 1.31 mmol/L)*			iMg (0.44 - 0.60 mmol/L)*		
	1.1 CIR†	1.4 CIR	1.6 CIR	1.1 CIR	1.4 CIR	1.6 CIR
1	0.93	0.87	0.81	0.45	0.37	0.34
2	0.98	0.9	0.88	0.43	0.34	0.36
3	0.92	0.9	0.82	0.41	0.35	0.33
4	0.90	0.87	0.75	0.40	0.36	0.27
5	1.02	0.86	0.84	0.44	0.36	0.35
6	0.93	0.8	0.79	0.39	0.32	0.31
7	0.88	0.84	0.73	0.40	0.37	0.30
Mean value (mmol/L)	0.95	0.86	0.80	0.43	0.35	0.32
Mean decrease (%)	23%	30%	33%	26%	37%	39%

* Reference range.
 † CIR = mg per kg per minute.

DISCUSSION

We demonstrated that rapid, continuously increasing serum citrate levels occur during plateletpheresis procedures in healthy donors and that these increased citrate levels are associated with mean peak reductions of up to 33 percent in iCa and 39 percent in iMg at the end of the procedure. Both the pace and magnitude of the decreases in ionized divalent cation levels were directly correlated with increasing CIRs. Furthermore, the frequency and severity of donor symptoms were closely associated with greater CIRs and higher serum citrate levels.

All three CIRs used in this study were within the recommended guidelines of the apheresis device manufacturer, and they spanned the range commonly used during plateletpheresis but were associated with continued and progressive accumulation of serum citrate. Significantly greater processed volumes and component yields were obtained at the

faster processing rates, but they were accompanied by progressive decreases in ionized divalent cation levels as serum citrate increased. Although donor symptoms were variable in this small cohort, the severity of citrate symptoms increased with increasing CIRs, and 33 percent of donors experienced uncomfortable muscle cramps and paresthesias at the greatest CIR. The decreases in iCa and iMg, and the increases in serum citrate levels and quantities of citrate administered during these procedures approach levels observed in massive transfusion during liver transplantation.^{13,14}

When ionized divalent cation levels were expressed as a fraction of total levels (FiCa, FiMg), the fractional decrease also exhibited a strong negative correlation with serum citrate levels. This finding has implications for the use of prophylactic supplemental oral or IV calcium, because, at a given serum citrate concentration, an increase in total serum calcium levels would be expected to lessen the absolute decrease in ionized levels.

In contrast to the constant, negative correlation between iCa and iMg and the progressive changes in serum citrate levels, changes in iPTH did not parallel the course of changes in those values. Levels of iPTH peaked early in plateletpheresis and then declined, despite further decreases in iCa. Furthermore, because peak iPTH responses occur as early as 5 to 10 minutes after the initiation of citrate-induced hypocalcemia,¹⁵ the maximal iPTH level probably occurred before the first 30-minute samples were obtained in this study.¹⁰ While previous studies have examined changes in the c-terminal and

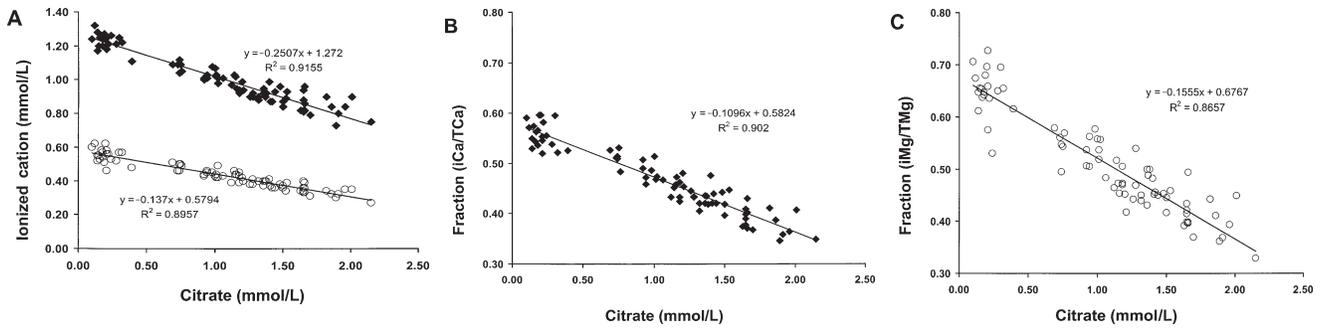


Fig. 2. Relationship between serum citrate concentrations and iCa (◆) and iMg (○) (A) and their fractions expressed as FiCa = (iCa)/[total Ca] (B) and FiMg = (iMg)/[total Mg] (C). Correlations with serum citrate for iCa ($R^2 = 0.92$), iMg ($R^2 = 0.90$), FiCa ($R^2 = 0.90$), and FiMg ($R^2 = 0.87$) were highly significant ($p < 1 \times 10^{-9}$ for all).

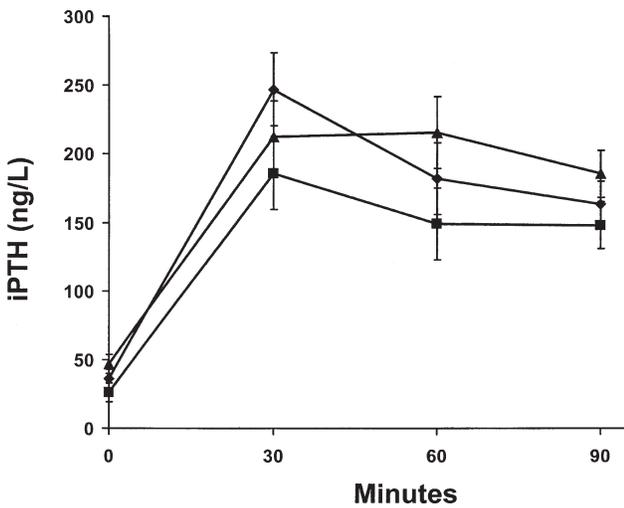


Fig. 3. Levels of iPTH during plateletpheresis. There were no differences in iPTH levels in procedures performed at a CIR of 1.1 (▲), 1.4 (■), or 1.6 (◆) mg per kg per minute, despite marked differences in iCa and iMg (see Fig. 2). Levels of iPTH were highest at 30 minutes and then declined, despite progressive decreases in iCa and iMg. Error bars are the standard error of the mean.

n-terminal regions of PTH,^{9,16,17} changes in iPTH may more accurately reflect physiologic responses.¹⁰ Although markedly increased iPTH levels have previously been noted during plateletpheresis,¹⁰ the relationship of these changes with controlled variations in CIRs was not examined until the present study. Our observations support the view that iPTH is released from the parathyroid gland as an initial bolus, which is followed by tonic secretion.¹⁵ The fact that we observed no significant difference in peak or subsequent iPTH levels during procedures performed at different CIRs suggests that the threshold for maximal release of iPTH is exceeded during routine plateletpheresis. It is also possible that the need for further PTH release is modified by the contribution of other compensatory mechanisms.

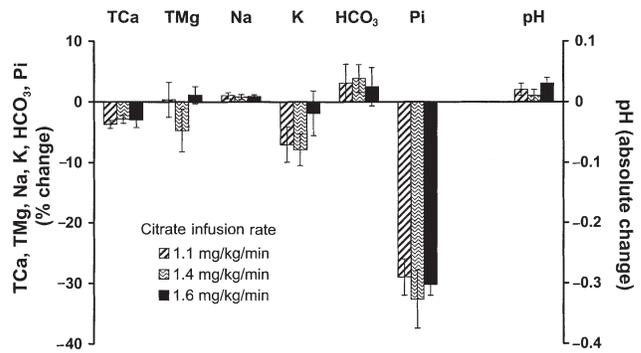


Fig. 4. Comparison of the effect of the infusion of citrate anticoagulant and preservative solution on serum analyte levels at the completion of plateletpheresis and on the levels before plateletpheresis. Changes for total calcium (TCa), total magnesium (TMg), sodium, potassium, bicarbonate, and phosphorus are expressed as the percentage of change on the left axis. Changes in pH are shown as the absolute change (serum pH at completion – serum pH before plateletpheresis) on the right axis. Significant changes at the completion of plateletpheresis from levels at baseline were observed for phosphorus ($p < 0.000001$), TCa ($p < 0.00001$), potassium ($p = 0.01$), bicarbonate ($p < 0.04$), sodium ($p < 0.0005$), and pH ($p < 0.02$). No significant change was observed for TMg ($p = 0.42$). Error bars are the standard error of the mean.

Serum phosphorus levels decreased markedly during plateletpheresis, with nadirs significantly below the normal range. Significant but more modest changes were observed in other serum analytes, with values at the end of plateletpheresis remaining within normal limits. Total calcium and potassium levels decreased by 3 and 6 percent, while serum sodium and bicarbonate increased by 1 and 3 percent, respectively. Similarly, serum pH increased from 7.40 to 7.42. No significant change was observed in total magnesium levels. In contrast to the changes in ionized divalent concentrations, changes in those values did not ex-

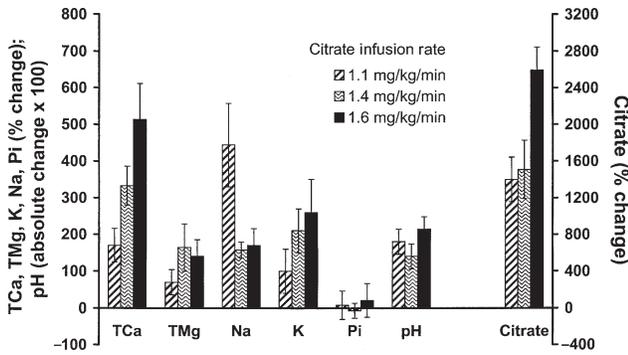


Fig. 5. Comparison of the effect of the infusion of citrate anticoagulant preservative solution on changes in urinary excretion of total calcium (TCa), total magnesium (TMg), sodium, potassium, phosphorus, and citrate and in urine pH before and at the completion of plateletpheresis. Urinary excretion was calculated by dividing the urine electrolyte concentration by the urine creatinine concentration in each sample. The axis for citrate is on the right and that for other analytes is on the left. Changes in excretion of TCa, TMg, potassium, sodium, phosphorus, and citrate are expressed as a percentage of the changes. Changes in urine pH are expressed as the pH in samples after plateletpheresis minus the pH before plateletpheresis ($\times 100$ for the scale of the axis). Mean urinary excretion increased significantly for citrate ($p < 0.00001$), TCa ($p < 0.00001$), TMg ($p < 0.001$), sodium ($p < 0.00004$), and potassium ($p < 0.00004$). Urinary phosphorus excretion did not increase significantly ($p = 0.18$). The mean urine pH increased by 2.0 units, from 5.6 before to 7.6 after plateletpheresis ($p < 0.000001$), which corresponded to a 99-percent decrease in hydrogen ion concentration. Error bars are the standard error of the mean.

hibit a clear association with serum citrate concentrations or changes in CIRs. These events may reflect the interactions of multiple compensatory mechanisms, such as hepatic and renal metabolism of citrate to bicarbonate, sustained increases in iPTH, and physiologic responses to the acute dextrose and sodium load infused as part of the anticoagulant solution.

We observed that plateletpheresis was accompanied by striking increases in urinary pH and urinary excretion of citrate, total calcium, total magnesium, sodium, and potassium, as measured in urine samples obtained at the beginning and end of each procedure. Paradoxically, the increased urinary excretion of calcium and magnesium occurred at a time when serum ionized divalent cation levels were markedly decreased and compensatory mechanisms for cation conservation, such as PTH release, should have been maximized. In agreement with prior observations that urinary iCa levels decrease after plateletpheresis,¹² we showed that urinary calcium and magnesium concentrations were much greater than urinary citrate concentration before plateletpheresis, while urinary citrate concentration increased in the ratio

TABLE 4. Molar ratios of urinary cations to urinary citrate before and after plateletpheresis

Cation	Cation:citrate (mmol/L)		Decrease*	
	Before	After	Percentage	p value
Calcium	1.99 ± 0.35	0.30 ± 0.04	80 ± 3	0.0002
Magnesium	1.83 ± 0.27	0.14 ± 0.12	91 ± 2	0.00002
Sodium	37.3 ± 5.5	3.73 ± 0.33	87 ± 2	0.00003
Potassium	20.4 ± 2.4	2.74 ± 0.30	85 ± 2	0.00003

* Calculated as described in Materials and Methods.

when measured against urinary calcium and magnesium concentrations after plateletpheresis. Our data suggest that renal excretion of an acute citrate load is associated with an obligate increase in cation excretion during plateletpheresis that cannot be overcome by the body's compensatory mechanisms. Sodium and potassium excretion also increased after plateletpheresis, which may reflect citrate's metabolism to bicarbonate and/or the delivery of sodium and dextrose with the infusion of the anticoagulant solution.

The aggregate data in this study provide new information about changes that occur during plateletpheresis and clarify the time course of previously described events. These findings are consistent with observations that symptoms increase markedly and citrate levels continue to increase when CIRs > 1.0 mg per kg per minute are used during plateletpheresis.⁷ While plateletpheresis is safe and well tolerated during most donations, this safety may be related to the fact that the procedures are completed, or modified because of donor symptoms, before the accumulation of toxic levels of citrate. Because higher CIRs must be used in lighter-weight donors during procedures performed at standard blood-processing rates, those donors will have more profound laboratory changes and associated symptoms. Oral or IV calcium administration in association with citrate infusions may provide a further level of donor comfort and permit increased component yields. Additional studies to ascertain the cumulative effects of these changes may be of benefit, particularly for frequent platelet donors.

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