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## Cardiovascular Depression Secondary to Ionic Hypocalcemia during Hepatic Transplantation in Humans

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Cardiovascular function, serum ionized calcium ( $\text{Ca}^{+2}$ ), and serum citrate were measured intraoperatively in patients ( $n = 9$ ) undergoing orthotopic hepatic homotransplantation. Serum citrate increased 20-fold ( $P < 0.0006$ ) following transfusion of citrated blood products in the absence of a functional liver. Serum ionized calcium decreased ( $P < 0.003$ ) with concomitant decreases in cardiac index ( $P < 0.005$ ), stroke index ( $P < 0.004$ ), and left ventricular stroke work index ( $P < 0.001$ ). Hemodynamic depression and ionic hypocalcemia were reversed following the administration of  $\text{CaCl}_2$ . In contrast to patients with normal hepatic function, who may tolerate large amounts of citrated blood, patients with end-stage liver disease demonstrate acute ionic hypocalcemia with concomitant hemodynamic depression when receiving citrated blood products during the course of hepatic transplantation. (Key words: Ions, calcium: cardiovascular performance. Liver: citrate; metabolism; transplantation. Transfusions: citrate, hypocalcemia.)

THE NUMBER OF patients undergoing orthotopic hepatic homotransplantation has greatly increased over the last 3 yr, primarily because of the introduction of cyclosporin.<sup>1</sup> Typically such surgery is associated with transfusions of large amounts of citrated bank blood.<sup>2</sup> Because citrate is metabolized mainly by the liver, and patients undergoing hepatic transplantation usually have decreased hepatic metabolic function, the citrate loading associated with massive transfusion of citrated blood products may induce

ionic hypocalcemia, creating myocardial depression despite adequate cardiac filling pressures. However, citrate intoxication (defined as hemodynamic depression associated with ionic hypocalcemia and elevated citrate levels) during liver transplantation has not previously been reported.<sup>3</sup> In part, this may be due to the relatively recent development of the calcium ion electrode for clinical applications. This study was performed to define the relationships between massive transfusion of citrated blood, serum citrate and serum ionized calcium, and cardiovascular function.

### Methods

Following approval by the Institutional Review Board for Biomedical Research, nine consecutive patients undergoing hepatic transplantation were studied. The mean body weight was 64.2 kg. All patients had end-stage hepatic failure associated with abnormal clotting studies (table 1). Bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), prothrombin time (PT), and citrate levels were elevated above the normal range in all patients.

Anesthesia was induced with ketamine and maintained with isoflurane and oxygen. All patients had an arterial catheter, a thermodilution flow-directed pulmonary arterial catheter, and a Foley catheter inserted. Because large volumes of fluid must be transfused rapidly during hepatic transplantation, blood products were administered via two 8F intravenous cannulae. A roller pump device with a 3-l reservoir was used for rapid administration of warmed blood products at flow rates of up to 2 l/min. The pump was primed with a blood replacement mixture of approximately two units of red blood cells (RBC) preserved with citrate, phosphate dextrose-adenine, two units

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TABLE 1. Medical Diagnosis and Relevant Pretransplantation Laboratory Results

Patient	Diagnosis	Total Bilirubin (mg/dl)	SGOT (U/l)	SGPT (U/l)	PT (s)	Ca <sup>+2</sup> (mmol/l)	Citrate (mmol/l)
1	Primary biliary cirrhosis	6.4	214	113	12.8	.90	.34
2	Chronic active hepatitis	1.9	66	28	13.9	1.11	.43
3	Primary biliary cirrhosis	22.4	81	27	14.8	1.08	.13
4	Primary biliary cirrhosis	10.2	3292	1011	17.3	1.08	.14
5	Drug-induced hepatic toxicity	2.6	60	123	13.0	.93	.04
6	Primary biliary cirrhosis	15.6	143	280	—	.90	1.0
7	Chronic active hepatitis	20.0	345	248	15.8	1.42	.92
8	Chronic active hepatitis	32.0	66	29	18.1	1.12	1.14
9	Chronic active hepatitis	3.8	193	134	12.6	.87	.75
Mean ± SE		12.7 ± 3.4	495 ± 350	221 ± 103	14.7 ± 0.7	1.04 ± 0.05	0.54 ± 0.1

SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; PT = prothrombin time.

of fresh frozen plasma (FFP), and 1,000 ml of Plasmalyte®, which yielded 2.0 l of volume with a hematocrit of 25%. Intraoperatively, patients received blood in amounts sufficient to maintain a hematocrit of 25%.

The technique of orthotopic hepatic hemotransplantation has been described in detail elsewhere.<sup>4</sup> Briefly, the hepatic artery and portal veins are dissected (Stage 1) and clamped, thereby making the patient functionally anhepatic. Simultaneously, the inferior vena cava is cross-clamped and a nonheparinized veno-venous bypass is instituted<sup>5</sup> (Stage 2). The recipient liver is excised and the recipient hepatic artery, suprahepatic, and infrahepatic vena cavae, and portal veins are anastomosed to the donor liver. Finally, the biliary anastomosis is performed (Stage 3), hemostasis is attempted, and the procedure is completed.

Blood samples were obtained for citrate and Ca<sup>+2</sup> measurements before hepatic devascularization (Stage 1), during the anhepatic period (Stage 2), after revascularization (Stage 3), and at the end of the procedure. The following cardiovascular variables were measured: mean arterial blood pressure (Pa), pulmonary artery pressure (Ppa), pulmonary artery occlusion pressure (Ppao), right atrial pressure (Pra), heart rate (HR), and cardiac output. Cardiovascular variables and Ca<sup>+2</sup> were measured at the beginning of surgery (baseline) and whenever the patient experienced systemic hypotension (Pa < 65 mmHg) despite adequate cardiac filling pressure (Ppao > 10 mmHg). CaCl<sub>2</sub> was administered through a central catheter in doses of 10–15 mg · kg<sup>-1</sup> to treat the hypotension, and a subsequent set of cardiovascular measurements were made 5–30 min after the administration of CaCl<sub>2</sub>. Cardiac output was measured in triplicate using 10 ml 20° C saline by the thermodilution technique. Citrate was assayed by the technique described by Warty *et al.*<sup>6</sup>

Citrate and ionized calcium were measured also in the pump reservoir. Core temperature was recorded

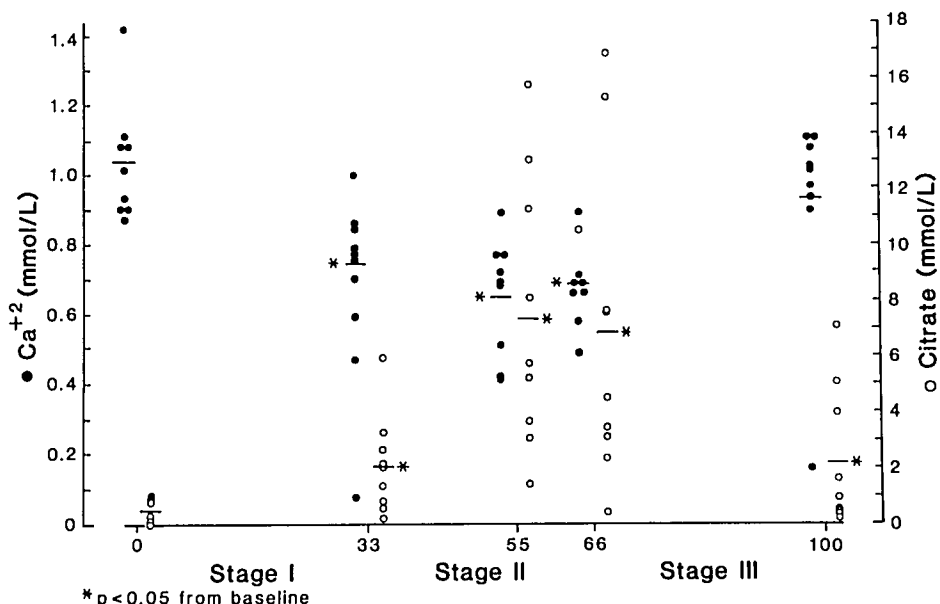
throughout the surgical procedure. Stroke index (SI), cardiac index (CI), left ventricular stroke work index (LVSWI), and systemic vascular resistance index (SVRI) were calculated using standard formulas. All data were analyzed using Student's *t* test for paired samples or by repeated measures analysis of variance. Statistical significance reports a *P* value of less than 0.05. All data are presented as mean ± SE.

## Results

Ionized calcium progressively decreased as citrate increased throughout the course of surgery. There was an inverse correlation between Ca<sup>+2</sup> and citrate for all patients. The greatest decline in Ca<sup>+2</sup> occurred during the anhepatic stage (*P* < 0.05). Serum Ca<sup>+2</sup> returned to normal levels by the end of the procedure. This sequence is illustrated in figure 1. Once serum citrate increased above 5 mmol · l<sup>-1</sup>, Ca<sup>+2</sup> did not decrease, reflecting the effect of calcium chloride replacement therapy. For all data points with citrate less than 5 mmol · l<sup>-1</sup>, the regression equation was: Ca<sup>+2</sup> = 1.01 – 0.59 citrate mmol · l<sup>-1</sup>, where *r* = 0.6 with *P* < 0.0001.

Decreases in CI, SI, and LVSWI paralleled the decrease in Ca<sup>+2</sup> despite no significant change in Ppao, Pra, pH, or SVRI. Core temperature decreased from 36.0° C to 33.6° C (*P* < 0.05) at the lowest values of cardiovascular function (table 2). These values of cardiovascular function were observed either during the anhepatic period or within the first hour of the postanhepatic period. Cardiovascular function returned to baseline values following normalization of Ca<sup>+2</sup> by CaCl<sub>2</sub> administration, although core temperature remained depressed at 33.5° C (table 2). Repeated boluses of CaCl<sub>2</sub> were often required during the procedure because of recurring hypotension despite adequate cardiac filling pressures. Our previous experience suggested that a bolus dose of 10–15 mg · kg<sup>-1</sup> of CaCl<sub>2</sub> was necessary to treat the hypotension. Blood re-

FIG. 1. Levels of serum ionized calcium ( $\text{Ca}^{+2}$ ) and citrate in patients in the three stages of hepatic transplantation. The stages of surgery are defined as per cent of time elapsed in operation. Serum  $\text{Ca}^{+2}$  was found to be inversely proportional to serum citrate concentration, with the greatest decrease in  $\text{Ca}^{+2}$  occurring during the peri-anhepatic stage of the procedure.



placement and the amount of calcium chloride administered for all patients are summarized in table 3. No dysrhythmic effects were observed during routine clinical monitoring following  $\text{CaCl}_2$  administration.

Citrate level in the mixture used to prime the blood infusion pump was  $30 \text{ mmol} \cdot \text{l}^{-1}$ . Citrate concentration in the RBC was  $60 \text{ mmol} \cdot \text{l}^{-1}$  and in FFP was  $60 \text{ mmol} \cdot \text{l}^{-1}$ .  $\text{Ca}^{+2}$  level in the pump mixture was zero, re-

flecting the anticoagulant effects of the citrate in citrated banked blood.

Acid-base balance was maintained by exogenous  $\text{NaHCO}_3$  administration (arterial  $\text{pH} > 7.35$ ). Although core temperature decreased from  $36.0^\circ \text{C}$  to  $33.5^\circ \text{C}$  during the anhepatic period, core temperature returned to baseline values by the end of the procedure.

## Discussion

In the presence of end-stage hepatic dysfunction, transfusion of citrated blood products dramatically increases serum citrate levels and results in ionic hypocalcemia and cardiovascular depression. Hepatic transplantation has created a unique opportunity to study the hemodynamic effects of ionic hypocalcemia in humans. In this study, the decrease in  $\text{Ca}^{+2}$  was associated with a de-

TABLE 2. Relationship Between Ionized Calcium and Cardiovascular Function

	Baseline	Nadir	Posttreatment with $\text{CaCl}_2$
$\text{Ca}^{+2}$ ( $\text{mmol} \cdot \text{l}^{-1}$ )	$1.04 \pm 0.06$	$0.56 \pm .03^*$	$1.02 \pm .04^\ddagger$
CI ( $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ )	$4.75 \pm 0.5$	$3.59 \pm 0.4^*$	$5.0 \pm 0.3^\ddagger$
SI ( $\text{ml} \cdot \text{m}^{-2}$ )	$55 \pm 4.1$	$44 \pm 4.3^*$	$56 \pm 5.3^\ddagger$
LVS WI ( $\text{g} \cdot \text{m} \cdot \text{m}^{-2}$ )	$46 \pm 4.2$	$31 \pm 3.1^*$	$49 \pm 4.9^\ddagger$
SVRI ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ )	$1184 \pm 153$	$1481 \pm 312$	$1352 \pm 364$
Pa (mmHg)	$74 \pm 3.9$	$66 \pm 5.0$	$76 \pm 4$
Ppao (mmHg)	$11.6 \pm 1.7$	$13.2 \pm 1.7$	$12 \pm 2.0$
Pra (mmHg)	$9.5 \pm 1.0$	$10.6 \pm 2.5$	$9.1 \pm 1.8$
pH	$7.40 \pm 0.02$	$7.36 \pm 0.02$	$7.38 \pm 0.02$
Temperature ( $^\circ \text{C}$ )	$36.2 \pm .22$	$33.6 \pm .30^*$	$33.5 \pm .33^\ddagger$

CI = cardiac index; SI = stroke index; LVS WI = left ventricular stroke work index; SVRI = systemic vascular resistance index; Pa = mean arterial blood pressure; Ppao = pulmonary artery occlusion pressure; Pra = right atrial pressure.

All values are mean  $\pm$  SE.

\*  $P < 0.05$  baseline to nadir.

†  $P < 0.05$  baseline to posttreatment.

‡  $P < 0.05$  nadir to posttreatment.

TABLE 3. Blood Replacement and Calcium Chloride Administration during Hepatic Transplantation (n = 9)

Replacement Product	Amount Given
Total $\text{CaCl}_2$ administered (g)	$4.3 \pm 2.2$
RBC administered (units)	$39.3 \pm 16$
FFP administered (units)	$33.4 \pm 11$
$\text{CaCl}_2$ /total CBP transfused ( $\text{g} \cdot \text{unit}^{-1}$ )	$0.05 \pm 0.01$
$\text{CaCl}_2$ /kg body weight/CBP transfused ( $\text{mg} \cdot \text{kg}^{-1} \cdot \text{unit}^{-1}$ )	$0.78 \pm 0.15$

RBC = red blood cells; FFP = fresh frozen plasma; CBP = citrated blood products.

Values are mean  $\pm$  SE.

crease in CI, SI, and LVSWI, despite adequate Ppao, Pra, and unchanged SVRI. Previous animal studies have shown that  $\text{Ca}^{+2}$  levels less than  $0.54 \text{ mmol} \cdot \text{l}^{-1}$  are associated with ventricular dysfunction,<sup>7,8</sup> and levels of  $0.10 \text{ mmol} \cdot \text{l}^{-1}$  with mechanical ventricular arrest.<sup>9</sup> Although the clinical relationship between ionic hypocalcemia and cardiovascular function in humans is controversial,<sup>10-15</sup> our study shows a decrease in  $\text{Ca}^{+2}$  to  $0.56 \text{ mmol} \cdot \text{l}^{-1}$  was associated with depressed cardiovascular function. It is possible that in previous clinical studies changes in  $\text{Ca}^{+2}$  were either transient or minimal, leading to a lack of equilibration between extracellular  $\text{Ca}^{+2}$  and intracellular calcium ion, which may explain the lack of correlation between cardiovascular function and serum  $\text{Ca}^{+2}$ . In contrast, in our study serum  $\text{Ca}^{+2}$  remained depressed for a substantial period of time during the anhepatic phase of the procedure. This may have allowed enough time for intracellular calcium ion to decline to a critical level, which subsequently altered cardiovascular function. We found that hemodynamic function improved following the normalization of serum  $\text{Ca}^{+2}$ . Presumably intracellular  $\text{Ca}^{+2}$  was also normalized, which subsequently returned cardiovascular function to baseline values. This study quantitatively defined what has been qualitatively described by Aldrete *et al.*<sup>3</sup>: that  $\text{CaCl}_2$  is required during hepatic transplantation to treat ionic hypocalcemia and the resultant cardiovascular depression. Most of the  $\text{CaCl}_2$  was administered during the anhepatic period when serum  $\text{Ca}^{+2}$  was lowest, reflecting that this was the most critical time for cardiovascular depression.

Although we attempted to keep constant other factors known to affect cardiovascular function, such as blood pH and cardiac filling pressures, we were unable to keep body temperature constant. Core temperature decreased from  $36.0^\circ \text{C}$  to  $33.6^\circ \text{C}$  ( $P < 0.05$ ) at the nadir of cardiovascular function. However, with restoration of  $\text{Ca}^{+2}$  posttreatment, cardiovascular variables returned to baseline values despite persistent hypothermia ( $33.5^\circ \text{C}$ ). It is unclear to what extent this degree of hypothermia may have affected calcium myocardial interaction; however, because hypothermia persisted posttreatment, it appears that the primary determinant of the cardiovascular depression was ionic hypocalcemia.

Citrate can avidly bind to  $\text{Ca}^{+2}$ , thereby decreasing serum levels of calcium ion. Loss of blood high in  $\text{Ca}^{+2}$  and its subsequent replacement with transfused blood low in  $\text{Ca}^{+2}$  may also have decreased serum  $\text{Ca}^{+2}$ , independent of citrate loading. In the postanhepatic period, the release of calcium from the citrate molecule as a function of citrate metabolism may have contributed to the normalization of serum  $\text{Ca}^{+2}$ . The mobilization of bound calcium from bone by parathyroid hormone may also have played a

role. Citrate metabolism may be affected by many factors, including tissue perfusion, acid-base status, body temperature, and the activity of aconitase, an enzyme responsible for the metabolism of citrate to cisaconitic acid and isocitric acid.<sup>10</sup> Aconitase exists principally in the liver, but may also be found in minor amounts in both muscle and renal cortex.<sup>8</sup>

The elevated citrate levels found at the end of the preanhepatic period in this study probably represent decreased citrate metabolism in the presence of moderate citrate loading by transfusion of citrated blood. The decrease in citrate metabolism is probably related to the poor hepatic function seen in all of our patients. During the anhepatic phase, serum citrate levels remained elevated (fig. 1), presumably because transfused blood products were high in citrate content and the absence of a functional liver prevented adequate citrate metabolism. Citrate began to decrease after hepatic revascularization and approached baseline values 5 h after revascularization. This may reflect the time necessary for the newly transplanted liver to become functional, because citrate clearance by the normally functioning liver is usually quite rapid.<sup>13</sup> Decreases in body temperature decrease citrate metabolism. The decrease in body temperature seen in our patients may have contributed to an initial increase in citrate level. Also, the elevation of body temperature to normal following hepatic revascularization may have contributed to the more rapid decay of serum citrate by the end of the procedure.

In summary, infusion of citrated blood products during hepatic transplantation results in citrate-induced ionic hypocalcemia with resultant cardiovascular depression. Treatment with  $\text{CaCl}_2$  improves cardiovascular function by reversing the ionic hypocalcemia. The frequent assessment of hemodynamic function and of serum ionized calcium levels is essential in managing the intraoperative care of patients undergoing orthotopic hepatic homotransplantation or patients with end-stage liver dysfunction who require large quantities of citrated blood products.

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