Cardiovascular Depression Secondary to Ionic Hypocalcemia during Hepatic Transplantation in Humans

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Cardiovascular function, serum ionized calcium (Ca²⁺), 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 CaCl₂. 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.¹ Typically such surgery is associated with transfusions of large amounts of citrated bank blood.² 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.³ 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 thermodynam 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-adrenaline, two units
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. 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 (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 Ca⁴⁺ 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 arterial occlusion pressure (Ppao), right atrial pressure (Pra), heart rate (HR), and cardiac output. Cardiovascular variables and Ca⁴⁺ 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). CaCl₂ was administered through a central catheter in doses of 10–15 mg·kg⁻¹ to treat the hypotension, and a subsequent set of cardiovascular measurements were made 5–30 min after the administration of CaCl₂. 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.⁶

Citrated 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 Ca⁴⁺ and citrate for all patients. The greatest decline in Ca⁴⁺ occurred during the anhepatic stage (P < 0.05). Serum Ca⁴⁺ 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⁻¹, Ca⁴⁺ did not decrease, reflecting the effect of calcium chloride replacement therapy. For all data points with citrate less than 5 mmol·L⁻¹, the regression equation was: Ca⁴⁺ = 1.01–0.59 citrate mmol·L⁻¹, where r = 0.6 with P < 0.0001.

Decreases in CI, SI, and LVSWI paralleled the decrease in Ca⁴⁺ 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 Ca⁴⁺ by CaCl₂ administration, although core temperature remained depressed at 33.5°C (table 2). Repeated boluses of CaCl₂ 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⁻¹ of CaCl₂ was necessary to treat the hypotension. Blood re-
FIG. 1. Levels of serum ionized calcium (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 Ca\(^{2+}\) was found to be inversely proportional to serum citrate concentration, with the greatest decrease in 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 CaCl\(_2\) administration.

Citrate level in the mixture used to prime the blood infusion pump was 30 mmol·l\(^{-1}\). Citrate concentration in the RBC was 60 mmol·l\(^{-1}\) and in FFP was 60 mmol·l\(^{-1}\). Ca\(^{2+}\) level in the pump mixture was zero, reflecting the anticoagulant effects of the citrate in citrated banked blood.

Acid–base balance was maintained by exogenous NaHCO\(_3\) administration (arterial \(\rho\)H > 7.35). Although core temperature decreased from 36.0\(^\circ\) C to 33.5\(^\circ\) 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 Ca\(^{2+}\) was associated with a decrease in p\(\rho\)H.

**TABLE 2. Relationship Between Ionized Calcium and Cardiovascular Function**

<table>
<thead>
<tr>
<th>Ca(^{2+}) (mmol·l(^{-1}))</th>
<th>Baseline</th>
<th>Nadir</th>
<th>Posttreatment with CaCl(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l·min(^{-1})·m(^{-2}))</td>
<td>4.75±0.5</td>
<td>3.59±0.4</td>
<td>5.0±0.3†</td>
</tr>
<tr>
<td>SI (ml·m(^{-2}))</td>
<td>55±4.1</td>
<td>44±4.3</td>
<td>56±5.3†</td>
</tr>
<tr>
<td>LVSWI (g·m·m(^{-2}))</td>
<td>46±4.2</td>
<td>31±3.1</td>
<td>49±4.0†</td>
</tr>
<tr>
<td>SVRI (dyn·s·cm(^{-2})·m(^{-2}))</td>
<td>1184±153</td>
<td>1481±312</td>
<td>1352±364</td>
</tr>
<tr>
<td>Pa (mmHg)</td>
<td>74±3.9</td>
<td>66±5.0</td>
<td>76±4</td>
</tr>
<tr>
<td>Ppa (mmHg)</td>
<td>11.6±1.7</td>
<td>13.2±1.7</td>
<td>12±2.0</td>
</tr>
<tr>
<td>Pph (mmHg)</td>
<td>9.5±1.0</td>
<td>10.6±2.5</td>
<td>9.1±1.8</td>
</tr>
<tr>
<td>(p)H</td>
<td>7.40±0.02</td>
<td>7.36±0.02</td>
<td>7.38±0.02</td>
</tr>
<tr>
<td>Temperature ((^\circ) C)</td>
<td>36.2±2.2</td>
<td>33.6±3.0</td>
<td>35.3±3.3†</td>
</tr>
</tbody>
</table>

CI = cardiac index; SI = stroke index; LVSWI = left ventricular stroke work index; SVRI = systemic vascular resistance index; Pa = mean arterial blood pressure; Ppa = pulmonary artery occlusion pressure; Pph = right atrial pressure.

All values are mean±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)**

<table>
<thead>
<tr>
<th>Replacement Product</th>
<th>Amount Given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CaCl(_2) administered (g)</td>
<td>4.3±2.2</td>
</tr>
<tr>
<td>RBC administered (units)</td>
<td>39.3±16</td>
</tr>
<tr>
<td>FFP administered (units)</td>
<td>33.4±11</td>
</tr>
<tr>
<td>CaCl(_2)/total CBP transfused (g·unit(^{-1}))</td>
<td>0.05±0.01</td>
</tr>
<tr>
<td>CaCl(_2)/kg body weight/CBP transfused (mg·kg(^{-1})·unit(^{-1}))</td>
<td>0.78±0.15</td>
</tr>
</tbody>
</table>

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

Values are mean±SE.
crease in CI, S1, and LSVWI, despite adequate PpaO, Pra, and unchanged SVRI. Previous animal studies have shown that Ca\(^{+2}\) levels less than 0.54 mmol·L\(^{-1}\) are associated with ventricular dysfunction,\(^7\)\(^ -\)\(^8\) and levels of 0.10 mmol·L\(^{-1}\) with mechanical ventricular arrest.\(^9\) Although the clinical relationship between ionic hypocalcemia and cardiovascular function in humans is controversial,\(^10\)\(^ -\)\(^15\) our study shows a decrease in Ca\(^{+2}\) to 0.56 mmol·L\(^{-1}\) was associated with depressed cardiovascular function. It is possible that in previous clinical studies changes in Ca\(^{+2}\) were either transient or minimal, leading to a lack of equilibration between extracellular Ca\(^{+2}\) and intracellular calcium ion, which may explain the lack of correlation between cardiovascular function and serum Ca\(^{+2}\). In contrast, in our study serum Ca\(^{+2}\) remained depressed for a substantial period of time during the anhepic 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 Ca\(^{+2}\). Presumably intracellular 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.\(^5\): that CaCl\(_2\) is required during hepatic transplantation to treat ionic hypocalcemia and the resultant cardiovascular depression. Most of the CaCl\(_2\) was administered during the anhepic period when serum 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\(^\circ\) C to 33.6\(^\circ\) C (P < 0.05) at the nadir of cardiovascular function. However, with restoration of Ca\(^{+2}\) posttreatment, cardiovascular variables returned to baseline values despite persistent hypothermia (33.5\(^\circ\) 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 Ca\(^{+2}\), thereby decreasing serum levels of calcium ion. Loss of blood high in Ca\(^{+2}\) and its subsequent replacement with transfused blood low in Ca\(^{+2}\) may also have decreased serum Ca\(^{+2}\), independent of citrate loading. In the postanhepic period, the release of calcium from the citrate molecule as a function of citrate metabolism may have contributed to the normalization of serum 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 aconitate, an enzyme responsible for the metabolism of citrate to cisaconitic acid and isocitric acid.\(^16\) Aconitate exists principally in the liver, but may also be found in minor amounts in both muscle and renal cortex.\(^8\)

The elevated citrate levels found at the end of the preanhepic 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 anhepic 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.\(^15\) 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 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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References


