Renal Sodium Handling With Cyclosporin A and FK506 After Orthotopic Liver Transplantation


ABSTRACT

Hypertension is common after orthotopic liver transplantation and may be due, in part, to cyclosporin A–induced renal dysfunction and/or enhanced proximal tubular sodium reabsorption. To determine whether enhanced proximal tubular sodium reabsorption is central to the development of posttransplant hypertension, measurements of renal hemodynamics and fractional clearances of lithium and sodium were compared 1 month after orthotopic liver transplantation in previously normotensive patients receiving either cyclosporin A (N = 24) or FK506 (N = 18), an immunosuppressive agent that is structurally unlike cyclosporin A and that has a lower reported incidence of hypertension. Median prednisone doses were 20 and 13 mg/day in the cyclosporin A and FK506 groups, respectively (P < 0.05). At 1 month, mean arterial blood pressure was higher in the cyclosporin A versus the FK506 group: 108 ± 2 versus 95 ± 3 mm Hg (P < 0.05). GFR, RBF, and renal vascular resistance were not different between the two groups: 59 ± 4 and 53 ± 5 mL/min per 1.73 m², 439 ± 28 and 440 ± 41 mL/min per 1.73 m², and 22,429 ± 1,822 and 22,977 ± 3,506 dyne s/cm² per 1.73 m², respectively. Fractional lithium excretion was similar in the cyclosporin A and FK506 groups: 19.9 ± 2.2 and 19.4 ± 2.0% (P = not significant) although both values were lower than those of normal controls (25.5 ± 1.1%) (P < 0.05). Fractional sodium excretion was 2.7 ± 0.3 and 2.3 ± 0.4% in the cyclosporin A and FK506 groups, respectively (P = not significant). These results indicate that proximal sodium reabsorption is enhanced to a similar degree during treatment with either cyclosporin A or FK506 after orthotopic liver transplantation and cannot per se explain the different incidence of hypertension between the two groups.

Key Words: Cyclosporin A, FK506, sodium, transplantation, hypertension

The development of hypertension is a common occurrence in cyclosporin A (CsA)-treated recipients of solid organ transplants (1–4). The incidence of hypertension in previously normotensive liver or heart transplant recipients has been reported to be 80 to 90% (3,5,6). CsA can also exacerbate preexisting hypertension in renal transplantation recipients (2,7,8).

The mechanism(s) of this de novo hypertension is thought to be, in part, related to the intense renal vasoconstriction and reduced GFR observed in most transplant recipients receiving CsA (9–11). Sustained renal vasoconstriction in turn results in enhanced sodium reabsorption in the proximal nephron, therefore leading to a form of “salt-sensitive” hypertension (12). Indeed, CsA-associated hypertension recently has been proposed as a model that underscores the pivotal role of the kidney in human essential hypertension (13).

Liver transplant recipients provide a model of posttransplant hypertension in which the kidney is not itself an allograft. To determine if enhanced proximal tubular sodium reabsorption plays a role in the development of hypertension within the first months after orthotopic liver transplantation (OLT), we measured renal hemodynamics and fractional lithium clearance (a surrogate marker of proximal sodium reabsorption) in CsA-treated OLT recipients. These results were compared with those of OLT recipients treated with FK506, a new immunosuppressive agent that is associated with degrees of renal vasoconstriction and reduced GFR similar to those with CsA, but with a significantly lower incidence of hypertension in most (14,15) but not all (16) reports. If sodium reabsorption is central to the development of hypertension, one might expect less proximal sodium reabsorption in patients treated with FK506. Our findings of equivalent degrees of enhanced proximal sodium reabsorption in both groups of patients instead suggest that the increased systemic blood pressure observed early after transplantation in CsA-treated OLT recipients cannot be explained solely by enhanced proximal sodium reabsorption.

PATIENTS AND METHODS

Forty-nine patients who underwent OLT at the Mayo Clinic form the basis of this report. No patient had a pretransplant...
history of hypertension, and no patients were receiving antihypertensive or diuretic medications during this study. Patients were monitored locally after hospital discharge during the first month after transplantation. Renal hemodynamic and clearance studies were undertaken between Days 16 and 50 posttransplantation. Patients were instructed to ingest a 100-mEq sodium diet after OLT. The results in the CsA- or FK506-treated OLT recipients were compared with those in a group of 22 healthy male controls studied in the General Clinical Research Center at St. Mary’s Hospital while ingesting a daily diet containing 10 mEq of sodium and 100 mEq of potassium for 7 days, followed by 200 mEq of sodium and 100 mEq of potassium for 7 days. The procedures and protocol for this study were reviewed by the institutional review board of the Mayo Clinic. Informed, written consent protocol for this study were reviewed by the institutional review board of the Mayo Clinic. Informed, written consent was obtained.

Immunosuppression Protocol

Immunosuppression for the CsA group consisted of 2 to 3 mg/kg CsA per day iv beginning on the second postoperative day until oral intake was established, after which CsA, 5 to 7 mg/kg per day iv, was administered in divided doses with the objective of maintaining trough blood levels between 250 and 450 ng/mL for the first 4 months posttransplantation. Prednisone doses were 200 mg/day initially and tapered to 20 mg/day by Day 30. Azathioprine, 2 mg/kg per day, was also administered. The regimen for FK506 patients consisted of FK506, 0.075 mg/kg, administered in a 4-h iv infusion every 12 h beginning 6 to 12 h after hepatic reperfusion, followed by oral dosing of 0.15 mg/kg twice daily with the dose adjusted to maintain trough plasma levels between 4 and 15 ng/mL. The regimen for FK506 patients also included prednisone, 100 mg/day, tapered to 10 mg/day by Day 30, but did not include azathioprine.

Renal Hemodynamic and Electrolyte Clearance Protocols

A single dose of lithium carbonate, 600 mg, was administered orally at 10:00 p.m. on the evening before the renal hemodynamic and electrolyte studies. Arterial blood pressures were recorded at 5-min intervals by an automated oscillometric sphygmomanometer (Accutorr; Datascope, Paramus, NJ). GFR and effective RPF (ERPF) were determined by the clearance of 125-Iothalamate and para-aminohippurate (PAH), respectively. After a loading dose of 0.22 μCi/kg iohexol and 10 mg/kg PAH, a maintenance solution of PAH was infused at a rate of 1 mL/min over a 45-min equilibration period. Three precisely timed urine collections were obtained at 30-min intervals for clearance measurements. Plasma levels of iohexol and PAH were measured before and after each period; the mean value was used for calculation. Samples of plasma and urine for lithium, sodium, and potassium measurement were collected simultaneously with iohexol and PAH measurements.

Laboratory Methods

Renal Clearance Measurements. Serum and urinary concentrations of 125-Iothalamate were measured by scintillation counting in a two-channel gamma counter. PAH was measured by autoanalyzer. Clearances were calculated as UV/P where U = urinary concentration, V = urinary flow rate expressed in milliliters per minute, GFR was taken as the clearance of iohexol, ERPF was taken as the clearance of PAH. RBF was calculated as ERPF/1 − hematocrit. Both GFR and RBF were corrected for body surface area. Renal vascular resistance was calculated as mean arterial blood pressure/RBF times 80 dynes/cm² per square meter. Sodium and potassium concentrations were determined by flame photometry. Plasma and urine lithium concentrations were determined by atomic absorption spectrophotometry as previously described (17). Fractional excretion of sodium, potassium, and lithium was calculated as the clearance of each substance divided by the GFR.

CsA and FK506 Measurements. CsA was measured in whole blood by high-performance liquid chromatography, and FK506 was measured in plasma by enzyme immunoassay as previously reported (15,18).

Statistical Analyses

Results are expressed as mean ± SE except as noted. Overall comparisons between subject groups were evaluated by analysis of variance. Individual comparisons were made by the use of parametric or nonparametric methods as appropriate, with the Bonferroni correction for multiple tests (19). A P value of less than 0.05 was considered to represent statistical significance.

RESULTS

Clinical characteristics of both OLT groups are shown in Table 1. Mean daily CsA and azathioprine doses in the CsA group were 672 ± 80 and 129 ± 14 mg, respectively. The mean daily FK506 dose in the FK506 group was 11 ± 1 mg. Compared with the CsA group, the FK506 group was receiving a lower median prednisone dose, 20 ± 2 versus 15 ± 9 mg/day (P < 0.05), respectively.

Pretransplant hemodynamic and electrolyte excretion data were available in 22 patients (15 from the CsA group and 7 from the FK506 group), none of whom had active hepatitis; ALT, alanine aminotransferase, AST, aspartate aminotransferase.

Clinical characterization of OLT recipients treated with CsA or FK506

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CsA (N = 26)</th>
<th>FK506 (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 ± 1.7</td>
<td>50 ± 2.4</td>
</tr>
<tr>
<td>Gender, M:F</td>
<td>11:15</td>
<td>15:8</td>
</tr>
<tr>
<td>Pretransplant Diagnoses, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSC</td>
<td>9 (35)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>PBC</td>
<td>7 (27)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>CAH</td>
<td>4 (15)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (23)</td>
<td>7 (31)</td>
</tr>
<tr>
<td>Days Since OLT (range)</td>
<td>31 (16–50)</td>
<td>25 (19–33)</td>
</tr>
<tr>
<td>ALT (U/L; normal, 10 to 45)</td>
<td>97 ± 24</td>
<td>105 ± 28</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (U/L; normal, 50 to 150)</td>
<td>550 ± 130</td>
<td>505 ± 98</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.3 ± 0.1</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td>Median Prednisone Dose (mg/day)</td>
<td>20 ± 2</td>
<td>13 ± 9</td>
</tr>
<tr>
<td>CsA Level (ng/dL)</td>
<td>285 ± 23</td>
<td>6.9 ± 1.8</td>
</tr>
</tbody>
</table>

10 Data are means ± SE unless otherwise indicated. PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; CAH, chronic active hepatitis; ALT, alanine aminotransferase.
whom were taking diuretics (Table 2). Systolic blood pressures and renal vascular resistances were slightly higher in the FK506 group before transplantation. In comparison with normal subjects, these end-stage liver disease patients had reduced arterial blood pressures, GFR, RBF, and fractional excretion of lithium.

**Systemic Blood Pressures and Renal Hemodynamics**

Systemic blood pressures and renal hemodynamic data after transplantation are shown in Table 3. Both CsA and FK506 groups had higher blood pressures after OLT (pretreatment versus 1-month mean arterial pressure 78 ± 2 versus 108 ± 2 and 87 ± 3 versus 95 ± 3 mm Hg for the CsA and FK506 groups, respectively). Mean systolic blood pressures were higher in both OLT groups compared with controls, whereas the mean diastolic blood pressures and mean arterial pressures were significantly elevated only in the CsA group. Mean systolic blood pressures in the CsA group (147 ± 4 mm Hg) were higher than both controls (116 ± 2 mm Hg; *P < 0.05) and the FK506 group (130 ± 4 mm Hg; *P < 0.05), as has been reported elsewhere (3,5). Additionally, a higher percentage of CsA patients (84%) compared with FK506 patients (35%) (*P < 0.01) developed clinical hypertension (defined as multiple clinic readings ≥ 140/90 mm Hg and/or mean arterial pressure ≥ 107 mm Hg) and received antihypertensive medication by the fourth month after OLT. Mean GFR fell to 59 ± 4 mL/min per 1.73 m² in the CsA group and to 53 ± 5 mL/min per 1.73 m², which were both below pretransplant levels and below the control subjects. There was no difference in GFR between the CsA and FK506 groups. Similarly, RBF was reduced and renal vascular resistance was increased to similar degrees in both OLT groups compared with the control group (Table 3). Although group mean values did not differ between transplant immunosuppressive regimens, the fall in GFR in the FK506 group was more severe relative to RPF, resulting in lower filtration fraction (17.4 ± 0.9%) as compared with the CsA (19.6 ± 0.7%) (*P < 0.05) and control (19.8 ± 0.6%) (*P < 0.05) groups.

**Urinary Electrolyte Excretion**

Urinary excretion and renal clearance data for lithium, sodium, and potassium are summarized in Table 4. Mean fractional excretion of lithium was decreased equivalently in the CsA and FK506 groups compared with controls: 19.9 ± 2.2 and 19.4 ± 2.0 versus 25.5 ± 1.1% (*P < 0.05), respectively. Systemic blood pressures contrasted with fractional lithium clearances in all three study groups are shown in Figure 1. Mean fractional excretion of sodium was increased in the CsA and FK506 groups compared with controls: 2.7 ± 3 and 2.3 ± 4 versus 1.5 ± 1%, respectively, but this increase was significant only in the CsA group. Twenty-four-hour urinary sodium excretion was lower in the FK506 group compared with the CsA group and controls: 117 ± 17 versus 166 ± 16 and 198 ± 5, mEq/day, respectively. No significant differences in the fractional excretion of potassium were observed between the three groups, whereas twenty-four-hour urinary potassium excretion was reduced in the CsA and FK506 groups compared with controls: 65 ± 4 and 54 ± 8 versus 95 ± 4 mEq/day (*P < 0.05), respectively.

**DISCUSSION**

The results of these studies early after OLT demonstrate similar and substantial decrements in GFR and RBF, despite significantly higher blood pressures in the CsA-treated group compared with the FK506 group. Proximal tubular sodium reabsorption was enhanced to similar degrees, as reflected by fractional lithium clearance, in both the CsA and FK506 groups compared with controls. It should be emphasized that study patients were selected to exclude those receiving diuretic therapy after transplant. Hence, whole-body sodium balance was being achieved with enhanced fractional sodium excretion at tubular sites distal to the proximal tubule. Most important, the increase in arterial pressures during this early period was less in FK506-treated patients, despite these changes in glomerular filtration and sodium homeostasis.

The association of CsA with *de novo* systemic hypertension is recognized in solid organ transplantation (2,3,13), in bone marrow transplantation (20), and during nontransplantation uses such as autoimmune uveitis (9). The finding that CsA per se plays a central role in causing or exacerbating hypertension in organ transplant recipients is supported by the improve-

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**TABLE 2. Hemodynamic and renal clearance measurements before OLT**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CsA (N = 15)</th>
<th>FK506 (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>109 ± 3</td>
<td>121 ± 4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>63 ± 3</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>79 ± 3</td>
<td>85 ± 3</td>
</tr>
<tr>
<td><strong>Renal Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (mL/min per 1.73 m²)</td>
<td>88 ± 6</td>
<td>97 ± 10</td>
</tr>
<tr>
<td>RBF (mL/min per 1.73 m²)</td>
<td>668 ± 46</td>
<td>612 ± 79</td>
</tr>
<tr>
<td>RVR (dyne s/cm² per 1.73 m²)</td>
<td>10,535 ± 1,132</td>
<td>13,699 ± 1,265&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Urinary Electrolyte Excretion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE Li (%)</td>
<td>19.3 ± 2.9</td>
<td>20.1 ± 3.2</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>1.1 ± 0.2</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>11.9 ± 1.5</td>
<td>13.5 ± 2.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are means ± SE. MAP, mean arterial pressure; RVR, renal vascular resistance; FE Li, FENa, and FEK, fractional excretions of lithium, sodium, and potassium, respectively.

<sup>b</sup> *P < 0.05* versus CsA group.
TABLE 3. Systemic blood pressure and renal hemodynamic data after OLT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CsA (N = 26)</th>
<th>FK506 (N = 23)</th>
<th>Controls (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Salt Diet</td>
<td>Low-Salt Diet</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>147 ± 4&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>130 ± 4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>116 ± 2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>88 ± 2&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>78 ± 3</td>
<td>74 ± 2</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>108 ± 2&lt;sup&gt;b-d&lt;/sup&gt;</td>
<td>95 ± 3</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td>59 ± 4&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>53 ± 9&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>107 ± 4</td>
</tr>
<tr>
<td>RBF (ml/min per 1.73 m²)</td>
<td>439 ± 28&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>440 ± 41&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>826 ± 33</td>
</tr>
<tr>
<td>RVR (dyne s/cm² per 1.73 m²)</td>
<td>22,429 ± 1,822&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>22,977 ± 3,504&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>8,813 ± 419</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>19.6 ± 0.7</td>
<td>17.4 ± 0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.8 ± 0.6</td>
</tr>
</tbody>
</table>

* Data are means ± SE. MAP, mean arterial pressure; RVR, renal vascular resistance; BP, blood pressure.
*<sup>a</sup> P < 0.05 versus high-salt controls.
*<sup>b</sup> P < 0.05 versus FK506.
*<sup>c</sup> P < 0.05 versus low-salt controls.
*<sup>d</sup> P < 0.05 versus all other groups.

TABLE 4. Urinary electrolyte excretion after OLT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CsA (N = 26)</th>
<th>FK506 (N = 23)</th>
<th>Controls (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Salt Diet</td>
<td>Low-Salt Diet</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEL&lt;sub&gt;1&lt;/sub&gt; (%)</td>
<td>19.9 ± 2.2&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>19.4 ± 2.0&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>25.5 ± 1.1</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENA (%)</td>
<td>2.7 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.3 ± 0.4</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>24 h (mEq)</td>
<td>166 ± 16&lt;sup&gt;c&lt;/sup&gt;</td>
<td>117 ± 17&lt;sup&gt;b-d&lt;/sup&gt;</td>
<td>198 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEK (%)</td>
<td>19.7 ± 3.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16.6 ± 1.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20.6 ± 1.0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>24 h (mEq)</td>
<td>65 ± 4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>54 ± 8&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>95 ± 4</td>
</tr>
</tbody>
</table>

* Data are means ± SE. FEL<sub>1</sub>, FENA, and FEK represent fractional excretions of lithium, sodium, and potassium, respectively.
*<sup>a</sup> P < 0.05 versus low-salt controls.
*<sup>b</sup> P < 0.05 versus CsA.
*<sup>c</sup> P < 0.05 versus all other groups.

The development of the immunosuppressive agent FK506, which is structurally unrelated to CsA, provides an opportunity to examine further the role of renal vasoconstriction and impaired glomerular filtration in the pathogenesis of posttransplant hypertension. Remarkably, blood pressure and systemic vascular resistance measured 1 month after OLT are lower in FK506-treated compared with CsA-treated patients, despite similar degrees of renal vasoconstriction and impaired glomerular filtration (14). Similar blood pressure differences are evident by the use of overnight ambulatory blood pressure monitoring (32). The incidence of clinical hypertension during the first 4 months of therapy was 28 versus 78%, FK506 versus CsA, respectively (14), in close agreement with this series. In a recently completed, randomized, open label trial of FK506 versus CsA in liver transplantation at this institution, similar degrees of nephrotoxicity...
were observed at 1 month posttransplantation, whereas treated with CsA or FK506.

clearance (B) in normal controls and in OLT recipients with either immunosuppressive agent and arterial A comprehensive scheme by which CsA might produce demonstrated a trend toward an increased incidence of hypertension in the CsA group, although a definitive relationship between changes in the kidney and either immunosuppressive agent and arterial pressure is far less certain. Some investigators suggest that CsA effects on the kidney are inseparable from the changes in systemic blood pressure (1,13). A larger multicenter, randomized comparison between CsA and FK506 for liver transplantation also demonstrated a trend toward an increased incidence of hypertension in the CsA group, although a definition of "hypertension" was not provided (16).

The relationship between changes in the kidney and posttransplant arterial pressure is less certain. Some investigators suggest that CsA effects on the kidney are inseparable from the changes in systemic blood pressure (1,13). A comprehensive scheme by which CsA might produce systemic hypertension has been described by Luke and postulates a central role for CsA-associated renal vasoconstriction and sodium retention (1). As noted above, our data and previous renal studies in animals and humans during CsA administration demonstrate a consistent reduction in RBF and increase in renal vascular resistance, although the time course of this change is controversial. Some investigators indicate that a reduction in blood flow and/or GFR can be detected after a single dose in normal subjects (34), whereas others fail to detect significant changes for many days (36). This renal vasoconstriction is at least partially responsible for a reduction in GFR and may be reversed by the infusion of a renal vasodilator, such as dopamine (34). During prolonged administration, additional mechanisms may contribute to the deterioration of kidney function with CsA, including independent effects of CsA on the glomerular ultrafiltration coefficient, vasculopathy, direct tubular toxicity, and interstitial fibrosis (37-39).

Regardless of the pathogenic pathway, one result of intense renal vasoconstriction, according to Luke (1,13), is an increased filtration fraction resulting in enhanced proximal tubular sodium reabsorption, ultimately leading to extracellular fluid volume expansion. This leads to a "sodium-sensitive" form of systemic hypertension, perpetuated by an ongoing inability of the kidney to adequately excrete a sodium load, except at higher than normal renal perfusion pressures. Such a requirement for elevated renal perfusion pressures, therefore, leads to an elevated systemic blood pressure in the manner described by Guyton in his model of pressure natriuresis in human essential hypertension (40). Indeed, the salt sensitivity of blood pressure after transplantation has been demonstrated in hypertensive CsA-treated renal transplant recipients (12).

A number of arguments seriously challenge this model, however. Our results did not demonstrate an increased filtration fraction, which might account for enhanced proximal tubular sodium reabsorption. Furthermore, despite enhanced proximal tubular reabsorption in both FK506- and CsA-treated recipients, arterial pressures differed between the two. Both the absolute pressure levels and the changes in arterial pressure from pretransplant levels were less in the FK506 group than those in the CsA group.

If enhanced proximal tubular sodium reabsorption plays a primary role in the pathogenesis of CsA-associated hypertension, one might expect a lower lithium clearance in CsA-treated patients compared with that in those receiving FK506. This study found no such difference between the two groups. Additionally, our results identified that the whole-kidney fractional excretion of sodium was maintained despite enhanced proximal tubular sodium reabsorption. This latter finding implies increased sodium excretion by the distal nephron. To our knowledge, segmental urinary sodium excretion has not been studied previously in liver transplant recipients. Studies in the dog during acute and chronic CsA administration demonstrate a reduction in fractional sodium excretion (41). Studies performed in hypertensive human renal transplant recipients find a reduction in the fractional excretion of lithium in CsA-treated subjects (42), although similar levels of fractional sodium excretion are present in CsA- and azathioprine-treated subjects (12), despite different arterial blood pressures. Studies in renal transplant recipients are complicated by other processes affecting the allografted kidney, of course, including graft rejection, preservation injury, and transplant renal artery stenosis. However, taken together, several lines of evidence suggest that whole-

Figure 1. Systemic blood pressure (A) and fractional lithium clearance (B) in normal controls and in OLT recipients treated with CsA or FK506.
body sodium balance is maintained by distal nephron mechanisms not closely related to arterial pressure after renal transplantation.

This conclusion is supported by several other types of studies. Normal subjects given CsA for several days develop a rise in arterial pressure before any change in renal sodium handling can be detected, suggesting that direct effects of CsA on systemic hemodynamics are dissociated from its effects on the kidney early in the course of administration (43). Conversely, both liver and bone marrow transplant recipients developing hypertension have changes in RBF and glomerular filtration indistinguishable from those remaining normotensive (44,45). A small but important group of liver transplant recipients with sustained posttransplant hypertension during CsA administration resolve their hypertension to normal levels and discontinue antihypertensive medications entirely. These individuals have persistent reductions in kidney function and blood flow indistinguishable from those remaining hypertensive (45). Such observations in humans are consistent with the observation that, although impaired renal function and sodium excretion are regularly found in experimental models using CsA, animals rarely develop a rise in arterial pressure (3,41). All of these findings argue that the regulation of arterial pressure and systemic vascular tone is not intrinsically linked to changes in kidney function during CsA administration.

What are the mechanisms responsible for enhanced distal sodium excretion after liver transplantation? Circulating aldosterone levels were not measured in all patients. However, aldosterone levels are elevated in patients with end-stage liver disease and fall to similar degrees 1 month after transplant in both CsA- and FK506-treated patients, as we described previously (10,14). Plasma renin activity falls in parallel fashion. End-stage liver disease patients with cirrhosis have increased adrenergic nerve traffic and sympathetically mediated sodium retention that are sufficient to overcome the natriuretic effects of elevated atrial natriuretic peptide (46). Sympathetic nerve traffic as measured with microneurography falls after liver transplantation in CsA immunosuppressed patients (46), which may allow unopposed natriuresis at distal sites. Circulating endothelin levels are elevated in many patients before transplantation and remain modestly above normal levels at 1 month (10) and for years thereafter (47). Experimental studies indicate that a low-dose infusion of endothelin produces natriuresis in rats (48,49). This effect may be related to the inhibition of amiloride-sensitive sodium channels in the distal nephron. It should be emphasized, however, that when data regarding any of these factors are available, no differences between CsA and FK506 in the kidney are identifiable. This area warrants further investigation.

With respect to renal potassium handling after OLT, we found no difference in fractional potassium excretion in transplant recipients compared with controls. Twenty-four-hour urinary potassium excretion was equivalently reduced in both transplant groups, although modestly, compared with controls. These observations are supported by previous clinical reports indicating occasionally impaired tubular secretory mechanisms for both potassium and hydrogen ion, leading to hyperkalemia and/or renal tubular acidosis (50,51).

A potential limitation of this study is the assumption that lithium clearance accurately estimates proximal tubular sodium reabsorption. A large body of experimental evidence supports this assumption in humans, particularly in sodium-replete conditions (52,53), although a role for the distal nephron in lithium handling, particularly in humans, cannot be excluded completely.

If the degree of renal vasoconstriction, reduced GFR, increased proximal tubular sodium reabsorption, and global renal sodium handling is equivalent in both CsA- and FK506-treated liver transplant recipients, what then accounts for the differences in blood pressure observed between the two groups early after transplantation? The answer to this question remains unknown. Prednisone doses at 1 month were lower in the FK506 group, which may be a major factor. When considering the cumulative effects of reduced prednisone doses used throughout the protocol in the FK506 group, lower doses were used during the first year after transplant. As a corollary finding, late weight gains and cholesterol elevations were considerably more prominent in CsA-treated patients (54). It is possible that mechanisms of blood pressure control differ at different times after transplantation. Our studies address only the rise in blood pressure and changes in renal function during the first few months after transplantation during the onset of de novo hypertension. Changes that occur later may reflect different mechanisms. We have observed that, although clinical hypertension (using protocol-defined measurements as reported here) remains lower in FK506 patients at 1, 4, and 12 months after transplant, this is no longer the case by 2 yr after transplant. At that time, more than 50% of patients meet the criteria for hypertension, which is no longer different from that in the CsA group, although the number of patients monitored for this long is small. Hence, the model postulating a long-term role of the kidney and pressure natriuresis in posttransplant hypertension may have applicability to late times that it does not have at early times.

Taken together, these studies highlight the importance of the independent regulation of vascular resistance within the kidney and other vascular beds, particularly during the early period after liver transplantation. Studies aimed at elucidating the mechanisms of vascular control after transplantation must recognize the disparate effects of immunosuppressive regimens within the kidney and other resistance beds. Understanding the pathogenesis of early posttransplant hypertension will require understanding local
factors regulating vasoconstrictor tone that differ between immunosuppressive regimens using CsA and FK506 in humans and that are not directly related to renal function or sodium excretion.

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