Resolution of Posttransplant Hypertension After Liver Transplantation Despite Impaired Glomerular Filtration

Stephen C. Textor, Lora Schwartz, Vincent J. Canzanello, Russell Wiesner, Sandra J. Taler, Michael Porayko, Daniel J. Wilson, Ruud Krom, John C. Burnett, and J. Carlos Romero

S.C. Textor, L. Schwartz, V.J. Canzanello, R. Wiesner, S.J. Taler, M. Porayko, D.J. Wilson, J.C. Burnett, Department of Medicine, Mayo Clinic, Rochester, MN
R. Krom, Department of Transplantation Surgery, Mayo Clinic, Rochester, MN
J.C. Romero, Department of Physiology, Mayo Clinic, Rochester, MN


ABSTRACT

Hypertension developing after transplantation is characterized by widespread vasoconstriction including the kidney. Late resolution (mean, 29 ± 4 months) of posttransplant hypertension has been observed in 15 (Group I) of 278 subjects monitored after liver transplantation. These studies were undertaken to define the systemic and renal changes associated with resolution, as compared with a group matched for age, sex, and time after transplant who remained hypertensive (Group II; N = 15) or a group who never developed hypertension (Group III; N = 23). Blood pressure during resolution paralleled changes in the systemic resistance index, which fell from 3,052 ± 548 to 1,872 ± 205 dyne/s·cm²/m² (P < 0.01). GFR and RBF remained low, despite the resolution of hypertension, and renal vascular resistance did not change. Circulating endothelin levels remained above normal in all transplant recipients (Group I, 11.9 ± 3.0 versus normal subjects, 7.0 ± 1.1 pg/ml; P < 0.05), and urinary prostacyclin excretion was suppressed (880 ± 120 versus 2,247 ± 187 ng/day; P < 0.01). No hormonal differences were apparent between transplant groups. These results demonstrate the capacity for systemic vasodilatation to occur after transplantation, independent of vascular tone in the kidney. They further suggest that renal vasoconstriction and impaired GFR alone are not sufficient to explain de novo hypertension after transplantation.

Key Words: Hypertension, cyclosporine, endothelin, prostacyclin, kidney, thromboxane, liver transplantation

The development of hypertension after organ transplantation during the administration of cyclosporine (CSA) and prednisone is common and presents multiple clinical and theoretical challenges. Among these is the question of the role of disturbed renal function in its pathogenesis. A rise in blood pressure develops in virtually all clinical conditions in which CSA is used (1,2), sometimes with serious adverse consequences (3). This disorder is characterized by widespread vasoconstriction affecting many vascular beds, including the kidney (4).

The pathogenic mechanisms underlying posttransplant hypertension are not fully established. In most instances, vasoconstriction in the systemic vasculature and in the kidney develops in parallel. Some authors have proposed that vasoconstriction in the kidney leads to subtle impairment of sodium excretion and is the primary event causing posttransplant hypertension (5). Hence, this disorder is presented as a special example of impaired "pressure natriuresis," illustrating the central role of the kidney in blood pressure control as advocated by Luke and Guyton (6,7). Other studies suggest that widespread abnormalities of sympathetic adrenergic nervous activation or alterations in the local vascular production of vasoactive prostaglandins or endothelin may be the primary mechanisms producing hypertension (8–11).

Our studies have focused on changes in blood pressure after liver transplantation. Although all organ transplant recipients share features regarding immunosuppression, liver recipients generally have normal or low blood pressures before transplant. Furthermore, cardiac function is generally normal and studies of renal function are not confounded by problems associated with renal transplantation, such as preservation injury, renal allograft rejection, and transplant renal artery stenosis (12).

Most patients who develop posttransplant hypertension require antihypertensive therapy indefinitely. However, we have observed that some patients lose the requirement for antihypertensive therapy during prolonged follow-up. The purpose of this report is to examine hemodynamic, renal, and laboratory characteristics of such patients to clarify the roles of the kidney and local vascular control in this disorder.

METHODS

Patients

Fifty-three liver transplant recipients were selected from 278 patients monitored for more than 1 yr after transplant in the CSA hypertension unit at Mayo Clinic. Before transplant surgery, patients were admitted to the General Clinical Re-
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search Center for renal and hemodynamic measurements during the ingestion of a diet containing 100 mEq of Na⁺ and 80 mEq of K⁺, as previously described (13). After transplantation and hospital discharge, these patients were monitored in the CSA hypertension unit during the first month, then during scheduled return visits at 4 and 12 months. Body weights, medication doses, and serum chemistry values were recorded. Twenty-four-hour collections for urine sodium, creatinine, and protein excretion were performed. Hemodynamic studies were performed as described below. Thereafter, patients were seen yearly or as needed when blood pressure problems arose. The procedures for this study were approved by the institutional review board of the Mayo Foundation.

Posttransplant immunosuppression consisted of CSA (2 to 3 mg/kg iv, followed by doses to maintain trough levels between 150 and 250 ng/mL as measured by whole-blood HPLC), azathioprine (2 mg/kg), and prednisone (200 mg/day diminishing to 20 mg/day in the first month and to 10 mg/day after the second month) as previously described (14).

Clinic and home blood pressure readings were reviewed monthly, and antihypertensive medication adjustments were made as needed to maintain blood pressures less than 140/90 mm Hg. When blood pressures persisted below 130/80 mm Hg and/or symptoms suggestive of postural hypotension developed, a “step-down” approach to therapy led to a reduction of antihypertensive therapy. When blood pressures remained at these levels, medications were discontinued altogether. The following criteria were applied to identify patients with “resolved” hypertension (Group I): (1) hypertension developing after transplant must have required antihypertensive therapy through the first postoperative year; and (2) when antihypertensive agents were stopped, blood pressure must have remained below 140/90 mm Hg for at least 1 month. The average time between discontinuing antihypertensive medications and the index visit was 10.9 months (range, 1 to 26 months; three patients were studied at least 6 months). Fifteen such patients (5.4%) met these criteria from 278 subjects monitored beyond 1 yr. A second group (Group II) comprised 15 subjects selected to match Group I with respect to age, sex, and time after transplant, but they continued to require antihypertensive medications. Group III comprised 23 additional patients who had remained normotensive throughout their posttransplant course.

Hemodynamic Studies

Arterial blood pressures were recorded with an automated oscillometric sphygmomanometer (Accutorr, Datascope, Paramus, NJ) at 5-min intervals during the supine measurement of hemodynamics. Cardiac output was determined from heart rate, and stroke volume was measured by changes in thoracic electrical bioimpedance gated during systole with a commercially available unit (NCCOM-3, Bomed, Inc., Irvine, CA) as reported previously (15). Stroke volume and cardiac output measurements using electrical bioimpedance agree closely with thermodilution values under widely varying conditions, including liver transplantation (16). This instrument uses surface electrocardiogram electrodes applied at the base of the neck and at the base of the thorax. Care was taken to replace the electrodes at the same surface sites for each study. Average values were obtained for 12 cardiac cycles at midexpiration for heart rate, stroke volume, cardiac output, and thoracic impedance (2, ohms). Stroke volume was derived from dV/dt, measured during electrical systole by the formula of Kubicek et al. (17) with modifications by Sramek et al. (18). Thoracic size was estimated by the use of a nomogram based on body weight, height, and sex. The coefficient of variation for repeated determinations of stroke volume by this method was 4.5%. Cardiac output was determined as the stroke volume × heart rate and was expressed as cardiac index (CI = cardiac output/body surface area). Systemic vascular resistance index (SVRI) was derived from mean arterial pressure (MAP = diastolic pressure plus [systolic minus diastolic pressure]/3), and CI was defined as MAP/Ci x 80 dynes/cm²/m².

Renal and Hormonal Studies

Measurements of GFR and effective RPF were performed with an iv infusion of [125I]iothalamate and para-aminohippurate over three timed collection periods as previously described (13). RBF was calculated as effective RPF/(1 – hematocrit). The renal vascular resistance index (SVRI) was calculated as MAP/RBF (expressed as (liters per minute per 1.73 m²) x 80 dynes/cm²/m²). Plasma renin activity and the urinary excretion of prostacelyn (measured as the stable metabolite, 6-keto-prostaglandin [PGLI]), and thromboxane A2 (measured as the excretion of thromboxane B2) were determined by radioimmunoassay (13). Normal values for these measurements were obtained from subjects free of medical conditions participating in the Rochester Family Heart Study during conditions of known sodium intake, as reported elsewhere (15). Circulating endothelin values were determined by a sensitive radioimmunoassay (19).

Statistical Methods

Data for each visit were recorded in a computer data base by the use of CLINFO. Data were expressed as Mean ± SE unless otherwise indicated. A comparison between values at different time intervals was performed by repeated measures analysis of variance. Specific comparisons were then performed with Bonferroni test or Scheffe’s test. A comparison between groups was undertaken by the use of analysis of variance or nonparametric (Wilcoxon rank sum) methods as appropriate (20).

RESULTS

Clinical Data

Age, sex, pretransplant diagnoses, mean daily CSA dose, trough CSA blood levels, and daily prednisone doses are summarized for each group in Table 1. Cholestatic liver disease, including primary biliary cirrhosis and primary sclerosing cholangitis, was the most common indication for liver transplantation. No differences in these values were evident between Groups I, II, and III. The mean time after transplant for the resolution of hypertension in Group I was 29 ± 4 months. Liver tests, including bilirubin, albumin, and serum aspartate transaminase levels, were similar between the transplant groups.

Blood pressure measurements obtained serially before and after transplantation in Group I patients are shown in Figure 1. Blood pressures were low before transplantation (101 ± 3/57 ± 4 mm Hg) and rose progressively during the first weeks after transplantation to hypertensive levels (154 ± 7/94 ± 5 mm Hg; P < .01). During treatment, blood pressures fell to 128
TABLE 1. Age, sex, pretransplant diagnosis, and biochemical values of patients after liver transplantation

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40.7 ± 3.2</td>
<td>45 ± 2.6</td>
<td>49 ± 2.4</td>
</tr>
<tr>
<td>Male/Female</td>
<td>3/12</td>
<td>3/12</td>
<td>3/20</td>
</tr>
<tr>
<td>Liver Disease Diagnosis (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestatic: PBC/PSC</td>
<td>6</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Parenchymal</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other (atresia/cancer)</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Time after Transplant (months)</td>
<td>29 ± 4</td>
<td>30 ± 4</td>
<td>44 ± 5</td>
</tr>
<tr>
<td>CSA Level (mg/dL)</td>
<td>164 ± 23</td>
<td>129 ± 10</td>
<td>142 ± 12</td>
</tr>
<tr>
<td>CSA Dose (mg/day)</td>
<td>296 ± 30</td>
<td>302 ± 24</td>
<td>286 ± 26</td>
</tr>
<tr>
<td>Prednisone Dose (mg/day)</td>
<td>9 ± 0.5</td>
<td>9.8 ± 0.2</td>
<td>9.6 ± 0.3</td>
</tr>
<tr>
<td>Aspartate Transaminase (mU/L)</td>
<td>35 ± 8</td>
<td>29 ± 8</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.01 ± 0.14</td>
<td>4.06 ± 0.07</td>
<td>4.09 ± 0.05</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.94 ± 0.12</td>
<td>0.88 ± 0.17</td>
<td>0.96 ± 0.13</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.22 ± 0.10</td>
<td>1.42 ± 0.06</td>
<td>1.33 ± 0.09</td>
</tr>
</tbody>
</table>

Figure 1. Arterial pressures before and after orthotopic liver transplantation (Tx) in Group I subjects (N = 15). The shaded zone represents the range of normal blood pressures (BP) (140/90 mm Hg). Despite needing antihypertensive medications for at least a year after transplant, these subjects eventually maintained normal pressures without drug therapy (far right). HTN, hypertension; mo, months. See Text.

± 10/73 ± 7 mm Hg by the end of the first year. Antihypertensive medications consisted of dihydropyridine calcium channel agents (nifedipine XL) in 11 of 15 with or without a combined α/β-blocker (labetalol) in 10 of 15. Step-down therapy allowed the discontinuation of antihypertensive drugs in these subjects. During this period, CSA levels in Group I fell from 267 ± 61 (during antihypertensive therapy, Figure 1) to 164 ± 23 ng/dL (P < 0.01) at the time of resolution, whereas daily prednisone doses fell from 15 ± 2 to 9 ± 1 mg/day (P < 0.01).

Systemic hemodynamic measurements for Group I are illustrated in Figure 2 and for all groups in Table 2. CI values were elevated before transplant (7.6 ± 1.6 L/min per square meter) and fell to normal levels by 1 month after transplant. They rose slightly during antihypertensive therapy but returned to the normal range as hypertension resolved (4.32 ± 0.4 L/min per square meter). MAP and SVRI changed in closely parallel fashion. The rise in blood pressure after transplant therefore reflected a rise in systemic vascular resistance to levels above normal (925 ± 195 pretransplant to 3,052 ± 548 dyne/s/cm²/m²; P < 0.01), which subsequently fell during antihypertensive therapy. Resolution of posttransplant hypertension, therefore, was mediated by a reduction in peripheral vascular resistance (from a pretreatment value of 3,052 ± 548 to 1,872 ± 205 dyne/s/cm²/m²; P < 0.01). Comparison values for Groups II and III are summarized in Table 2. Pretransplant blood pressure, cardiac index, and systemic vascular resistance did not differ between these groups. Blood pressure and SVRI in Group III were lower than in either Group I or II 1 month after transplant. No differences were apparent at the late time, although only Group II was receiving antihypertensive medications. These medications in Group II consisted primarily of dihydropyridine calcium channel blocking agents (nifedipine XL) in 10 of 15 and diuretics in 5 of 15 cases. In 10 of 15 instances, these were combined with the α/β-blocker labetalol.

Renal Hemodynamics

GFR are shown in Figure 3 for each group as measured before transplant, at 1 month, and during late follow-up. RBF and RVRI are summarized in Table 2. Pretransplant GFR values were below those of normal subjects studied under similar conditions, as previously reported (15). GFR fell after transplantation in all groups (e.g., Group III, 86 ± 4 to 50 ± 6 ml/min at 1 month; P < 0.01) and remained at reduced levels thereafter. GFR did not differ between Groups I, II, and III at any time interval. Group I patients had a GFR of 66 ± 6 ml/min at the time of resolution of posttransplant hypertension, which did
Figure 2. Serial measurements of CI measured by thoracic electrical bioimpedance, MAP, and systemic vascular resistance in Group I patients. Pretransplant values reflect systemic vasodilation and hyperdynamic circulation in patients with end-stage liver disease. Shaded areas represent normal values obtained in participants in the Rochester Family Heart Study, as previously reported (15). Changes in MAP (upper panel) closely tracked changes in systemic vascular resistance. *De novo* hypertension (HTN) after transplantation was mediated by systemic vasoconstriction. The resolution of posttransplant hypertension represented a reversal of this effect. BP, blood pressure; OLtx, liver transplantation. See Text.

not differ from GFR values at 1 month after transplant (58 ± 7 mL/min). Serum creatinine values are summarized in Table 1 and did not differ between groups. Hence, renal function did not differ at any time between hypertensive patients after transplant and patients remaining normotensive.

Serial measurements of RVRI in Group I subjects are illustrated in Figure 4 and are compared with measurements of SVRI at the same times. RVRI rose from normal to markedly elevated levels after transplantation (11.421 ± 2.913 to 24.180 ± 2.107 dyne/s-cm²/m²; *P < 0.01), in parallel with the changes in SVRI. However, despite the resolution of posttransplant hypertension, RVRI remained elevated (20.767 ± 4.294 dyne/s-cm²/m²). Hence, the fall in arterial
pressure and systemic resistance during the resolution of hypertension was not accompanied by a comparable fall in renal resistance. Group III patients had a lower RVRI than the others 1 month after transplant, reflecting lower arterial pressures (Table 2). RBF was not different between any of these groups at any time. Renal vascular resistance in Groups II and III did not differ from Group I at the late time. As shown in Table 2, the proportion of cardiac output reaching the kidneys ranged between 4 and 6.8%, less than that of normal subjects (15%).

**Hormonal Measurements**

Measurements of plasma renin activity, aldosterone, and the urinary excretion of prostacyclin (as reflected by the metabolite 6-keto-PGF1α) and thromboxane B2 are shown in Table 3. Plasma renin activity and aldosterone values were normal for the levels of urinary sodium excretion. However, urinary prostacyclin (6-keto-PGF1α) was suppressed below normal values in all transplant recipients (e.g., Group 1, 880 ± 120 versus 2,247 ± 187 ng/day; P < 0.01). In contrast, urinary thromboxane excretion did not differ

**TABLE 3. Hormonal measurements after orthotopic liver transplantation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (N = 15): Resolved Posttransplant Hypertension</th>
<th>Group II (N = 15): Matched Hypertension Treated</th>
<th>Group III (N = 23): Never Hypertensive</th>
<th>Normal Subjects (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Renin Activity</td>
<td>1.14 ± 0.47</td>
<td>2.42 ± 1.05</td>
<td>0.8 ± 0.2</td>
<td>1.2 ± 0.45</td>
</tr>
<tr>
<td>Aldosterone (ng/dL)</td>
<td>18.3 ± 2.4</td>
<td>22 ± 3.7</td>
<td>16.8 ± 7</td>
<td>10.1 ± 1.2</td>
</tr>
<tr>
<td>6-keto-PGF1α (ng/dL)</td>
<td>880 ± 120b</td>
<td>795 ± 153b</td>
<td>902 ± 152b</td>
<td>2,247 ± 187</td>
</tr>
<tr>
<td>Thromboxane B2 (ng/dL)</td>
<td>1,334 ± 266</td>
<td>932 ± 140</td>
<td>1,174 ± 12</td>
<td>1,136 ± 655</td>
</tr>
<tr>
<td>Endothelin (pg/mL)</td>
<td>11.9 ± 3.0c</td>
<td>12.0 ± 2.5c</td>
<td>12.5 ± 2.0c</td>
<td>7.07 ± 1.11</td>
</tr>
</tbody>
</table>

* Values are mean ± SE.
* b P < 0.01 versus normal subjects.
* c P < 0.05 versus normal subjects.
from that of normal subjects. Circulating endothelin levels were elevated in all groups of liver transplant recipients (e.g., Group III, 12.5 ± 2.0 versus normal, 7.07 ± 0.13 pg/mL; P < 0.05). No differences in any of the above hormones were apparent between the three transplant groups.

**DISCUSSION**

These studies demonstrate for the first time that systemic vasoconstriction leading to elevated posttransplant blood pressures during CSA administration can return to normal. However, the reversal of systemic vasoconstriction in Group I subjects was independent of sustained renal vasoconstriction. Impaired glomerular filtration, suppression of urinary prostacyclin, and elevation of circulating endothelin also persisted in those subjects in whom systemic hypertension resolved. Furthermore, even patients who never developed posttransplant hypertension (Group III) had similar hormonal changes and impaired glomerular filtration during CSA administration. These results demonstrate independent and divergent regulation of systemic and renal vascular tone late after organ transplantation.

Our data extend previous studies regarding pathogenetic factors in de novo hypertension after liver transplantation. Nephrotoxicity and hypertension have been common since the introduction of CSA. Many authors have assumed that the two problems are closely related. Luke has proposed that CSA-induced hypertension represents a model of essential hypertension in some respects (5,6) and postulates that impaired glomerular filtration and sodium excretion are fundamentally responsible for the development of a sodium-sensitive form of hypertension (21). Although our studies cannot refute this paradigm, they challenge its premise and suggest that the regulation of RBF and glomerular filtration may be separated from blood pressure control after transplantation. Our results indicate that impaired glomerular filtration itself is not sufficient to lead to systemic hypertension, as reflected by patients in Group III, who remained normotensive despite reductions in GFR. Furthermore, the resolution of hypertension after transplant was not reflected within the renal vasculature or by detectable improvement in GFR.

Several other lines of evidence indicate that the control of systemic blood pressure and renal function after transplantation are not closely linked. Many experimental studies in the rat (22,23), dog (24), and rabbit (25) establish major abnormalities in renal function during CSA administration, which have been attributed to alterations in adrenergic tone and activation of the renin-angiotensin system and other hormonal pathways, including increased endothelin and thromboxane production (9,11,22,24,26–29). The development of systemic hypertension in these models is rare, however, indicating that, in nonhuman species, CSA-mediated effects on the kidney do not lead to hypertension. Conversely, CSA infusion in a sheep model produces a rise in blood pressure and systemic vascular resistance without measurable changes in kidney function (30). Hence, the control of regional vascular resistance in animals often does not parallel that in the human kidney.

Although nephrotoxicity and hypertension are common in all human transplant applications, they do not necessarily coincide. Patients remaining normotensive after bone marrow transplantation, for example, show decrements in glomerular filtration and RBF similar to those developing rapidly progressive hypertension (3). Patients treated with CSA for uveitis also demonstrate little relationship between GFR and hypertension, although RBF is higher after 1 yr in those remaining normotensive (31). Those observations agree with our results in Group III, in whom significant decrements in GFR and renal vasoconstriction were never associated with hypertension, despite a reduction in the renal excretion of urinary eicosanoids and increased endothelin (Table 3) of comparable magnitude to those of the other subjects.

Other differences in renal function, such as sodium excretory capacity, cannot be excluded as an explanation for the blood pressure differences between Groups I, II, and III. It may be relevant, however, to compare the effects of CSA with those of a structurally different immunosuppressive agent, FK506. FK506 produces decrements in RBF with renal vasoconstriction and suppression of urinary eicosanoid excretion at least as great as that observed with CSA (32). In these liver transplant recipients studied 1 month after transplantation, FK506 also enhances proximal tubular sodium reabsorption to the same degree as CSA, as reflected by the fractional excretion of lithium (33). Remarkably, FK506-based regimens are associated with de novo hypertension less commonly than CSA-based regimens under these conditions. The role of sodium excretion in posttransplant hypertension merits further study.

Most important, these studies establish the potential for the resolution of posttransplant hypertension. This occurred late after transplantation, despite the continuation of CSA and steroids. To our knowledge, no such resolution has been documented previously. It should be emphasized that this was not common. Group I patients represent only 5.3% of patients monitored for more than 1 yr after transplant. More than 80% of such patients are treated for hypertension, most of whom are treated indefinitely (2). Conclusions regarding this subgroup may not apply universally. Nonetheless, we believe that this group offers an important opportunity for mechanistic studies of vascular control after transplantation. Reversal of vasoconstriction was related temporally to reductions in CSA levels and steroid doses in Group I, although no differences were apparent between Groups I and II. These results agree with those of other studies that have demonstrated only crude relationships between either doses or CSA levels and toxic manifestations.
(34). Dosage effects in Group I cannot be separated completely from the effects of time after transplant. For that reason, data from normotensive patients in Group III are of particular value. Taken together, these data suggest that changes in vascular resistance can develop at any time and limit the extent of systemic vasoconstriction, regardless of events occurring in the kidney.

These observations extend previous conclusions reached during the treatment of posttransplant hypertension with dihydropyridine calcium channel blocking agents. These agents have been advocated as preferred agents for the treatment of posttransplant hypertension because of their vasodilatory properties (35–37). In some cases, these vascular effects appear to offer benefits regarding kidney function, particularly after renal transplantation (36). These results suggest that, regardless of whether systemic resistance returns to normal because of the spontaneous resolution of posttransplant hypertension (as in Group I) or under the influence of calcium channel blocking agents (as in Group II), intense renal vasoconstriction was unchanged, coupled with impaired production of vasodilatory prostanoids and impaired glomerular filtration.

The underlying mechanisms for persistent, perhaps permanent, alterations in the kidney during CSA administration are unknown but have been the topic of considerable concern (38). Our results underscore that such changes do not appear to be prone to spontaneous resolution, although other reports indicate that impaired GFR can improve somewhat when CSA is discontinued, even after long-term administration (39,40). Nonetheless, occasional progression to ESRD in cardiac transplant recipients and the demonstration of irreversible structural changes in animals raise the genuine issue that parenchymal kidney injury eventually supersedes hemodynamic changes during CSA administration (38,41). It may be speculated that, although late changes allow the relaxation of peripheral resistance vessels outside of the kidney, vessels within the kidney are altered in such a way that spontaneous reduction of vascular resistance cannot occur.

What changes in vascular control allow the spontaneous reduction of systemic resistance and blood pressure? Several studies indicate that CSA administration, particularly when combined with steroids, alters local vascular factors, such as the production of endothelin-derived relaxing factors, including nitric oxide (42) and prostacyclin (43). Similarly, the local production of vasoconstricting factors, such as endothelin or thromboxane A2, are enhanced in some situations. We propose that late changes in vascular regulation likely represent a reconstitution of one or more of these mechanisms in favor of less intense constriction. Whether intervention to increase the rate of such changes is possible remains to be seen. Recently published studies using fish oil supplementation early after renal and cardiac transplantation indicate that alterations in the fatty acid substrates for prostaglandin production, in fact, may allow meaningful changes in vascular tone and blood pressure control (44,45). Whether these effects consistently extend to the kidney is not yet certain.

Taken together, these studies provide additional data to indicate that renal and systemic vascular beds are regulated independently after liver transplantation. They indicate that sustained vasoconstriction in the kidney with impaired GFR and eicosanoid excretion persists, even in patients whose posttransplant hypertension eventually resolves. Further studies directed at the regulation of blood pressure and vascular control after transplantation must recognize the divergence of different vascular beds and the potential for major changes to develop at late intervals after transplant.

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