Hypertension developing in normotensive patients after organ transplantation is a common and important element of posttransplant care. It has been encountered primarily in the last decade since the introduction of cyclosporine A (CSA) as a major immunosuppressive agent. The entity of de novo hypertension in previously normotensive subjects should be distinguished from worsening preexisting hypertension after transplant, which is the case in most patients with end-stage renal disease, for example. For that reason, this article will focus on hypertension developing after liver transplantation.

Blood pressure rises in nearly all transplant recipients treated with CSA and steroids. Liver and cardiac transplant recipients, for example, develop hypertension needing therapy in 80% to 90% of cases. Medical management of the transplant recipient requires treating hypertension effectively while avoiding interactions between antihypertensive regimens and CSA.

Defining the mechanisms underlying this process represents a challenge, and an opportunity, for the hypertension community. Hypertension develops uniformly and rapidly in human subjects but rarely in animals. "Conventional" pressor mechanisms seen in other disorders, such as the circulating renin-angiotensin system, are not obviously disturbed in this disorder. Initial reports from the renal transplant literature dealt with hypertension primarily as an extension of cyclosporine nephrotoxicity, in which impaired kidney function and sodium retention produced volume expansion and "salt-sensitive" hypertension. However, subsequent data have indicated that nephrotoxicity and hypertension during cyclosporine administration are not absolutely linked. Our current hypothesis is that posttransplant hypertension represents primary abnormalities of vascular endothelial function. Thus, posttransplant hypertension may be a distinct form of acquired hypertension that merits close scrutiny.

In this discussion, we will review a case of acquired hypertension after liver transplantation. The clinical data are from studies undertaken in the cyclosporine clinic within the division of hypertension of the Mayo Clinic, Rochester, Minn.

Case Report

The patient was a 44-year-old white man with end-stage liver disease related to alcohol use. He worked 50 hours weekly as a maintenance supervisor. Sixteen months before evaluation, he discontinued alcohol after an episode of jaundice, ascites, and encephalopathy. One month before admission, he was noted to have anemia and melena. Endoscopic evaluation revealed grade II esophageal varices and congestive gastropathy. Ascites was present. He had noted progressive fatigue, pruritus, and leg cramps. There was no prior history of hypertension or diabetes. Medications consisted of 75 mg spironolactone three times daily, 40 mg furosemide daily, vitamin K supplementation, lactulose, sodium-free antacids, and multiple vitamins. There had been no recurrent episodes of encephalopathy.

Because of recurrent esophageal bleeding and muscle wasting, he was referred for evaluation for liver transplantation. On physical examination, he appeared emaciated. His weight was 72.4 kg; height, 173 cm; temperature, 36.9°C; pulse, 80 beats per minute; and blood pressure, 98/60 mm Hg. Scleral icterus and jaundice were present. Several cutaneous "spider" telangiectasias were noted. There was evident loss of muscle mass in the arms and shoulders. Gynecomastia was detected. There was shifting dullness and an abdominal fluid wave. Hepatic span was 7 cm to percussion. The spleen tip was palpable. There was a trace of lower extremity edema. Deep tendon reflexes were diminished. There was no asterixis, and his mental status was clear.

Laboratory data revealed a hemoglobin of 105 g/L with hematocrit of 30.3%. Mean cell volume was 105 fL. White blood count was 8.70 × 10^9/L and platelets 105 × 10^9/L. Sodium was 132 mmol/L and potassium 4.0 mmol/L. The prothrombin time was 14.9 seconds despite vitamin K supplementation. Total cholesterol was 3.15 mmol/L (122 mg/dL); triglycerides, 0.58 mmol/L (51 mg/dL); serum creatinine, 79.6 μmol/L (0.9 mg/dL); albumin, 30.9 g/L (3.09 g/dL); alkaline phosphatase, 70.3 μkat/L (422 U/L); AST, 2.13 μkat/L (128 U/L); and bilirubin, total, 164 μmol/L (9.6 mg/dL) and direct, 95.8 μmol/L (5.6 mg/dL). Levels of α1-antitrypsin, anti-nuclear antibody, anti-smooth muscle antibodies, and anti-mitochondrial antibodies and serum ferritin were...
unremarkable. Ceruloplasmin levels were normal. α-Fetoprotein was mildly elevated at 13.4 μg/L. Serological studies for hepatitis A, B, and C were negative. Upper gastrointestinal endoscopy demonstrated persistent esophageal varices. Abdominal ultrasound examination demonstrated a small liver, ascites, normal portal venous blood flow, and no intrahepatic mass.

After completion of the transplant evaluation, the patient underwent orthotopic liver transplantation. The resected liver specimen demonstrated Mallory bodies and regenerating hepatic nodules diagnostic of alcoholic cirrhosis. A small intrahepatic portal vein was thrombosed.

Transplant immunosuppression consisted of CSA administered intravenously at 3 mg/kg per day, methylprednisolone beginning at 3 mg/kg per day, and azathioprine at 2 mg/kg per day. Serial measurements of blood pressure are shown in Fig 1. The patient was discharged 16 days after transplant, taking 40 mg/d prednisone, 260 mg CSA b.i.d., and 150 mg/d azathioprine. CSA level was 171 μg/dL as measured by high-performance liquid chromatography on whole blood. CSA levels ranged between 276 and 157 ng/dL. Target levels were between 150 and 200 ng/dL during the first month. Four weeks after transplant, blood pressure was 160/98 mm Hg. Antihypertensive therapy was initiated with 100 mg labetalol b.i.d. and increased to 200 mg b.i.d.

The postoperative period during the initial months was complicated by several problems, as illustrated in Fig 1. The patient was hospitalized for cytomegalovirus infection between days 46 and 57. Blood pressure fell during this period, and labetalol was discontinued. Azathioprine was withheld and not restarted until day 99. Despite mobilization of ascites and edema with continued weight loss, blood pressure rose progressively to 170/108 mm Hg on day 57. Ambulatory blood pressure monitoring for 24 hours demonstrated sustained elevations without the usual nocturnal fall in pressure. Labetalol was restarted.

The patient was hospitalized again between days 73 and 99 with pneumonia and respiratory failure from *Pneumocystis carinii* pneumonia. Trimethoprim/sulfamethoxazole was administered intravenously. Prednisone dosage was tapered to 15 mg/day. Blood pressure again fell, and labetalol was discontinued during this episode. The patient was intubated and required ventilatory support for several weeks. Toward the end of this hospitalization, blood pressure rose again to levels of 178/116 mm Hg. CSA levels were between 66 and 146 ng/dL. Labetalol therapy was restarted, and 60 mg nifedipine XL was added, as shown in Fig 1.

A third hospitalization occurred in the fifth month, during which a stenotic biliary duct was dilated and a stent placed. The patient was discharged, taking 15 mg/d prednisone and 260 mg CSA b.i.d., with a CSA level of 118 ng/dL, and 150 mg/d azathioprine.

Home and office blood pressures remained 160/108 mm Hg. Antihypertensive therapy was advanced to 60 mg/d nifedipine XL and 200 mg labetalol t.i.d. Nifedipine was discontinued due to headache and edema. It was subsequently restarted at 30 mg daily. By the sixth month after transplant, pressure levels were 120/82 mm Hg.

Two years after transplant, the patient was taking 75 mg CSA b.i.d., 10 mg/d prednisone, and 150 mg/d azathioprine. Antihypertensive medications had been gradually discontinued 6 months before return. Blood pressure was 130/75 mm Hg. The patient appeared well, and surgical wounds were well healed. His weight was 66 kg. Laboratory testing revealed a creatinine level of 176 μmol/L (2.0 mg/dL), CSA level of 150 ng/dL, bilirubin of 30.8 μmol/L (1.8 mg/dL), albumin of 44 g/L (4.4 g/dL), cholesterol of 5.12 mmol/L (200 mg/dL), and triglycerides of 3.03 mmol/L (268 mg/dL). Glomerular filtration rate (GFR) measured by iothalamate clearance was 36 mL/min per 1.73 m².

Studies of systemic and renal hemodynamics and serial measurements of vasoactive hormones during this course are summarized in Tables 1 through 3. High cardiac output levels before transplant fell to normal afterward, and renal blood flow and GFR fell well below normal ranges. Considering the rise in arterial pressures, these changes reflected widespread vasoconstriction manifested as elevated systemic and renal vascular resistances.

**Discussion**

In summary, this patient had end-stage liver disease associated with low arterial pressures. After liver transplantation, mean blood pressure rose more than 50

**Fig 1.** Graph shows arterial pressure changes after liver transplantation in a man with alcoholic cirrhosis and ascites. Pressures rose from below normal to hypertensive levels within several weeks after transplantation and initiation of cyclosporine and steroid immunosuppression. Pressure continued to rise despite reduction in cyclosporine A and steroid doses. Body weight (not shown) rose immediately after transplantation but fell thereafter as edema and ascites resolved. Blood pressures fell during episodes of cytomegalovirus (CMV) infection and pneumocystis pneumonia but rose again after these conditions resolved. Antihypertensive medications consisting of labetalol and nifedipine were administered for nearly 2 years; the severity of hypertension abated thereafter.
liver transplantation likely represents reversal of the circulatory abnormalities associated with liver failure.

Second, the progressive rise in blood pressure to hypertensive levels within 4 weeks after transplant was characterized by an "overshoot" of peripheral vascular resistance. Posttransplant hypertension is characterized hemodyanmically by rapid development of widespread vasoconstriction. Examining changes in vascular resistance in these patients therefore requires some means of measuring cardiac output. We have used several noninvasive methods in such patients, including thoracic electrical bioimpedance and duplex ultrasonography, with remarkably consistent results. The results of serial measurements in the patient under discussion are summarized in Table 1. Simply measuring mean arterial pressure (which rose 76%) in this case underestimates the rise in peripheral resistance (+354%) during the first 4 weeks. Thus, understanding the pathogenetic mechanisms underlying vasoconstriction observed in this setting is a foremost concern.

Third, despite reduced GFR and renal blood flow, mobilization of sodium and volume occurred with the disappearance of ascites and edema without diuretics. Considering both the fall in blood flow and the rise in arterial pressure, renal vascular resistance rose twofold (202%) (Table 2). These observations present an apparent paradox: How can sodium mobilization develop in the presence of intense renal vasoconstriction and impaired filtration?

Taken together, these questions are fundamental to understanding de novo hypertension after transplantation. To address these issues, let us consider what is known.

### Clinical Features

Blood pressure rises modestly, but universally, soon after CSA is started. An example of this is shown as the average diastolic pressures of bone marrow transplant recipients treated with CSA (without steroids) for 3 days before transplantation (Fig 2). Most transplant recipients receive both CSA and steroids as immunosuppression. When steroids are added, pressure may rise further. Blood pressure rises in patients treated with CSA for nontransplant indications also, although less rapidly and less commonly. In these reports, patients often have preexisting hypertension or a positive family history of essential hypertension.

Accelerated hypertension with serious vascular injury has been described, including microangiopathic hemolysis, encephalopathy, and seizures. Intracranial hemorrhage has occurred. It is difficult to distinguish between the effects of high pressures per se and additional vascular injury induced directly by CSA. It may be relevant that serious hypertensive complications were unexpected. Preclinical studies in experimental animals did not suggest this would be a problem, and in fact, hypertension does not develop in the rat, dog, or rabbit treated with cyclosporine. The reasons for such species differences are not clear. Renal vasoconstriction and impaired sodium excretion have been observed in these animal models without changes in arterial pressure (Table 4). Studies during long-term CSA administration in rats and rabbits demonstrate acquired resistance to the vasoconstrictive effects of norepinephrine and an-

### Table 1. Serial Hemodynamic Values

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>Cardiac index ([L/min]/m²)</th>
<th>SVRI (dyne · s · cm⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretransplant</td>
<td>64</td>
<td>6.70</td>
<td>802</td>
</tr>
<tr>
<td>Week 1</td>
<td>93</td>
<td>4.73</td>
<td>1565</td>
</tr>
<tr>
<td>Week 2</td>
<td>95</td>
<td>7.18</td>
<td>1058</td>
</tr>
<tr>
<td>Week 3</td>
<td>105</td>
<td>3.19</td>
<td>2623</td>
</tr>
<tr>
<td>Week 4</td>
<td>118</td>
<td>2.61</td>
<td>3642</td>
</tr>
<tr>
<td>1 year</td>
<td>99</td>
<td>4.09</td>
<td>1947</td>
</tr>
<tr>
<td>Normal (mean±SD)</td>
<td>89±9</td>
<td>3.18±0.68</td>
<td>2325±487</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; SVRI, systemic vascular resistance. Noninvasive measurements (electrical bioimpedance) of MAP, cardiac index, and SVRI were obtained during intervals after liver transplant in 44-year-old man. For details regarding methods, see Reference 6.

mm Hg to sustained hypertensive levels for nearly 2 years. Interestingly, the hypertension resolved gradually thereafter despite persistent kidney dysfunction attributed to cyclosporine.

This case illustrates several important points that may help define the problem of posttransplant hypertension. Most transplant recipients have complex medical problems, as reflected by the cytomegalovirus infection and hospitalizations during the posttransplant period. Hence, it is difficult to study hypertension in isolation. Despite the complexities of each patient, the onset and characteristics of acquired hypertension are remarkably uniform even among different organ transplants. Hence, potent pressor mechanisms appear to assert themselves regardless of the clinical setting. Several issues related to this case warrant emphasis.

First, patients with advanced liver disease before transplantation have low blood pressures with elevated cardiac outputs. The mechanism is not certain but reflects vasodilatation developing within the splanchnic circulation. A detailed review of this disorder is beyond the scope of this article; however, it has been proposed that vasodilatation is a primary event, which leads to sodium retention by the kidney with subsequent volume expansion and ascites formation. Recent experimental studies in rat and canine models demonstrate that inhibition of nitric oxide synthesis can reverse these changes. Hence, the progressive rise in systemic resistance and return of cardiac output levels to normal after liver transplantation likely represents reversal of the circulatory abnormalities associated with liver failure. For further details, see Ref-
giotensin in the intact animal, which may explain the lack of blood pressure change.24,37,52 Furthermore, initial human studies with CSA were conducted in renal transplant recipients, most of whom have hypertension before transplant. The most severe clinical problems develop in previously normotensive subjects, often children, such as those receiving bone marrow or liver transplants.53-55 It appears that the severity of vascular injury relates more to the rate of change than to the absolute levels of arterial pressure. Similar observations have been made for hypertensive complications related to acute glomerulonephritis in children and in pregnancy.56,57 Specific conditions may predispose to vascular events, such as pretransplant whole-body radiation before bone marrow transplantation.58,59

Nocturnal hypertension and the loss of nocturnal fall in pressure are features of posttransplant hypertension.60 Studies in cardiac transplant recipients indicate that left ventricular hypertrophy develops as rapidly as 6 weeks,61 which has been attributed partly to this characteristic. Nocturnal headaches and reversal of day-night sodium excretion patterns are common. Preliminary data indicate that some patients later regain the nocturnal fall in pressure. The mechanism of this is not certain, although glucocorticoid administration or Cushing’s syndrome regularly produce the same effect. Some authors suggest that cardiac denervation may explain the loss of fall in cardiac transplant patients, but the same observation in other transplant settings makes this unlikely to be the sole mechanism.60

The natural history of this disorder is not well understood. Most commonly, antihypertensive medications are continued indefinitely, although the severity of hypertension varies. Hypertension does subside if CSA is discontinued.23,28,62 The case presented in this article illustrates a feature not previously emphasized. By 2 years after transplant, blood pressure had fallen to normotensive levels despite continuation of both CSA and steroids and discontinuation of antihypertensive medications. This is not common but has been observed in our clinic in 13 of 278 patients.

Pathogenesis

The mechanisms underlying CSA-induced hypertension are not fully known. This has been a particularly difficult question to study, because (1) results in humans differ markedly from results in animals, and (2) experimental models using CSA demonstrate renal and vascular changes but rarely develop hypertension. There appear to be major species effects regarding the cardiovascular actions of CSA. For the purposes of this discussion, we will focus primarily on human studies.

Hemodynamic studies suggest that elevated systemic vascular resistance, as observed in the patient presented in this article, is the underlying hemodynamic abnormality. This is also evident in cardiac transplant recipients studied beyond 1 year.63,64 What is the mechanism of elevated vascular resistance?

Abnormalities of Vasomotor Regulation

Table 4 contains a list of mechanisms for which data have been presented suggesting a role in CSA-induced vasoconstriction. As noted, considerable disparity exists between experimental and human studies. Contrary to studies in the rat and dog, for example, numerous human studies indicate that the circulating renin-angiotensin system is relatively suppressed in posttransplant hypertension.30,31 Measured plasma volumes in cardiac transplant recipients are slightly expanded.1,30 Blood pressures in renal transplant patients are sensitive to dietary sodium intake during CSA administration.24
Plasma renin activity remains relatively suppressed even during sodium restriction. This is supported by the relative lack of antihypertensive efficacy of angiotensin converting enzyme inhibitors when used alone. The possibility that local or tissue renin-angiotensin mechanisms participate in this disorder cannot be excluded. Few data are available to address this issue at present.

The role of adrenergic vasoconstriction is uncertain. Several experimental studies indicate that renal vasoconstriction and alterations in sodium excretion depend on renal sympathetic nerve activation. These effects can be reversed or prevented with renal denervation and adrenergic blocking agents. However, human renal transplants also demonstrate CSA-induced vasoconstriction immediately after transplant despite being denervated and adrenergic blocking agents. Human renal transplant recipients demonstrate a rise in urinary endothelin excretion, with no measurable change in circulating endothelin, 4 to 6 hours after CSA administration. This precedes a major, dose-related fall in renal blood flow and GFR after each oral dose. Whether this endothelin is actually responsible for the renal vasoconstriction during CSA therapy is not yet established.

Circulating endothelin levels are elevated in patients with end-stage liver disease. Our studies suggest that these levels increase further the first week after transplant, then return toward baseline but remain elevated after 4 weeks. Such a course was observed in the patient presented in this article (Table 3). This sequence differs from the progressive rise in vascular resistance during the 4 weeks after transplant. Hence, it is unlikely that endothelin alone regulates vasoconstriction in this setting. Nonetheless, these levels are distinctly abnormal. Suppressor doses of endothelin potentiate contractions to norepinephrine in human coronary

### Table 4. Mechanisms of Vasoconstriction After Transplantation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experimental model</th>
<th>Human studies</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic hypertension</td>
<td>No</td>
<td>Yes</td>
<td>5,24-27</td>
</tr>
<tr>
<td>Renal vasoconstriction</td>
<td>Yes</td>
<td>Yes</td>
<td>26-29</td>
</tr>
<tr>
<td>Renin-angiotensin system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased renin levels</td>
<td>Yes</td>
<td>No</td>
<td>29-34</td>
</tr>
<tr>
<td>Adrenergic nervous system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased activity</td>
<td>Yes</td>
<td>Yes/No</td>
<td>26,27,35,36</td>
</tr>
<tr>
<td>Increased sensitivity</td>
<td>Yes/No</td>
<td>?</td>
<td>24,37-39</td>
</tr>
</tbody>
</table>

Local vascular mechanisms

- Increased prostacyclin: Yes | Yes/No* | 40,41
- Increased thromboxane: Yes | Yes/No* | 7,42-47
- Increased endothelin: Yes | Yes    | 7,48
- Impaired EDRF: Yes | Yes* | 49-51

EDRF, endothelium-derived relaxing factor. There is considerable disparity between experimental and human studies regarding the mechanisms of vascular control altered by cyclosporine. This may be related to species differences as well as to the additional factors introduced by clinical transplantation, including routine steroid administration.

*Bulk of evidence favors this conclusion.

Studies in renal transplant recipients demonstrate a rise in urinary endothelin excretion, with no measurable change in circulating endothelin, 4 to 6 hours after CSA administration. This precedes a major, dose-related fall in renal blood flow and GFR after each oral dose. Whether this endothelin is actually responsible for the renal vasoconstriction during CSA therapy is not yet established.

### Table 5. Evidence for Endothelial Effects of Cyclosporine

<table>
<thead>
<tr>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>Elevated systemic vascular resistance</td>
<td>64,68</td>
</tr>
<tr>
<td>Elevated renal vascular resistance</td>
<td>7,65,66</td>
</tr>
<tr>
<td>Vascular injury</td>
<td></td>
</tr>
<tr>
<td>Elevated factor VIII antigen</td>
<td>69</td>
</tr>
<tr>
<td>Thrombotic-uremic syndrome</td>
<td>54,70</td>
</tr>
<tr>
<td>Microvascular thrombosis</td>
<td>7,72</td>
</tr>
<tr>
<td>Endothelial cell &quot;vasculization&quot;</td>
<td>73</td>
</tr>
<tr>
<td>Vascular endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>Impaired prostacyclin release</td>
<td>7,44,49</td>
</tr>
<tr>
<td>Increased release of endothelin</td>
<td>74</td>
</tr>
<tr>
<td>Impaired endothelium-derived vasodilation (EDRF)</td>
<td>49-51</td>
</tr>
</tbody>
</table>

EDRF, endothelium-derived relaxing factor.
vascular regulation after transplantation is profoundly altered by microvascular thrombosis \( ^{53,71,73} \) and persistent vasoconstriction. \(^{73} \) Parallel events in the kidney in the patient described in this article (Tables 1 and 2) and normalization of arterial pressures did not have the expected effect on CSA treatment. The kidney is particularly sensitive to this effect, and the mechanism underlying its sensitivity remains unclear. The evanescent nature of EDRF renders precise evaluation of this phenomenon difficult in humans. \(^{90} \) The role of EDRF in vascular regulation after transplant awaits further studies, particularly in human studies using inhibitors of EDRF, such as L-NMME, indicate that nitric oxide regulates blood pressure and blood flow tonically in normal animals. \(^{88,89} \) Sustained inhibition of EDRF produces vasoconstriction and hypertension. \(^{90} \) The evanescent nature of EDRF renders precise evaluation of this phenomenon difficult in humans. However, studies using subcutaneous fat vessels from humans treated with CSA indicate impaired endothelium-dependent vasodilation. \(^{49} \) Whether this reflects impaired EDRF release vasodilation or prostacyclin-dependent vasodilation is not certain.

These mechanisms are not mutually exclusive. Perhaps the most coherent synthesis of the available information is that vascular effects of CSA alter vasoactive functions of the endothelium generally. Studies in the dog indicate that vasomotor tone may depend finally on the relative activity of both vasodilating forces, such as EDRF, and vasoconstrictor effects, such as endothelin. Lerman and associates\(^{91} \) indicate that vascular effects of low doses of endothelin, which alone do not elevate arterial pressure, are potentiated during inhibition of EDRF with infused \( ^{14} \)-l-arginine-methyl ester.

Taken together, several lines of data indicate that vascular regulation after transplantation is profoundly altered (Table 5). In extreme forms of CSA toxicity, this may result in release of endothelium-derived factor VIII antigen, intravascular hemolysis, and finally, thrombosis with fibrin deposition in the microvasculature. \(^{53,67,68} \) In less severe forms, this means a tilt of vascular regulatory forces in favor of regional, and often widespread, vasoconstriction.

Are regional vascular beds affected equally? It appears not. The kidney is particularly sensitive to this process and demonstrates increased involvement, with both microvascular thrombosis \(^{53,71,73} \) and persistent vasoconstriction, despite changes in other vascular beds. It is of interest that a fall in systemic vascular resistance and normalization of arterial pressures did not have parallel events in the kidney in the patient described in this article (Table 1). There can be little doubt that renal vasoconstriction combined with exogenous glucocorticoids favors sodium retention. Some authors propose that abnormalities in sodium excretion related to enhanced afferent arteriolar vasoconstriction are central to the sustained rise in arterial pressure. \(^{42,92} \) However, a structurally different immunosuppressive agent, FK 506, produces at least as severe renal vasoconstriction but does not commonly produce de novo hypertension. \(^{93,94} \) Hence, renal and systemic vascular changes after transplantation may be dissociated, as they were in the patient discussed in this article (Tables 1 and 2). Factors responsible for differential sensitivity of the kidney are not yet understood. Pathological changes in the kidney during long-term CSA administration may become irreversible. \(^{95} \) Hence, although vasomotor abnormalities appear to be foremost early after transplant, permanent changes in renal structure may develop, and recovery of renal function when CSA is withdrawn may be incomplete. Although altered renal hemodynamics and sodium homeostasis participate in the development of hypertension after transplant, they do not alone explain the pathogenesis of this disorder. Other factors affecting the peripheral vasculature may predominate.

### Consequences of Posttransplant Hypertension

No data are available on the outcome of untreated hypertension in these conditions. Early experience with adverse hypertensive events, including intracranial bleeding and rapid development of left ventricular hypertrophy, leads to prompt intervention. Alterations in lipids, glucose homeostasis, and other factors may increase the cardiovascular risk in transplant recipients relative to the general population.

#### Treatment Considerations

The optimal antihypertensive therapy in this situation is not known. Several principles have emerged, however, during the years of experience with CSA.

First, the selection of antihypertensive agent should recognize the impairment of glomerular filtration and the vasoconstricted state of the kidney. Uric acid levels are elevated, sometimes to extreme levels. \(^{96,97} \) CSA occasionally inhibits potassium and hydrogen ion secretion. Diuretics often are avoided to prevent further azotemia and uric acid elevations. Potassium-sparing agents must be used with caution. Angiotensin converting enzyme inhibitors, as noted above, have limited efficacy when used alone and may aggravate both hyperkalemia and acidosis.

Second, the choice of antihypertensive agent must consider effects on CSA disposition. Several calcium channel blockers, particularly verapamil, diltiazem, and nicardipine, interfere with CSA removal and may lead to CSA accumulation. \(^{98-100} \) Under some circumstances, calcium channel blockers can be used to allow reduced CSA dosage, hence reducing the patient costs. If not considered and monitored closely, however, this effect commonly leads to unexpected episodes of CSA toxicity.

Calcium channel blocking agents have achieved the status of "preferred" drugs. This is partly related to their efficacy in smooth muscle vasodilation. The dihydropyridine class, in particular, can overcome even the potent vasoconstriction due to endothelin. \(^{101,102} \) Under experimental circumstances, verapamil appears to po-

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tentiate the immunosuppressive properties of CSA. Whether this is of clinical importance in humans is unknown. Nifedipine and isradipine have virtually no effects on CSA disposition and are potent vasodilators. Preliminary data indicate that other dihydropyridines may allow renal vasodilation during CSA therapy. Renal studies indicate that they prevent the intense renal vasoconstriction during long-term administration. Hence, they may have some rationale as primary agents. Diltiazem may further offer the advantage of preventing early graft failure in renal transplants. Recent studies suggest that coronary vascular disease after cardiac transplantation may be slowed by diltiazem. In our experience, blood pressure control after liver transplantation parallels the reduction in systemic vascular resistance. However, vasodilation in the systemic vasculature is not transmitted to the renal circulation in the form of improved glomerular filtration.

Other agents may be effective. Our experience indicates that labetalol may be used as primary therapy in many patients. Alternate β-blockers have been used. Some investigators have used angiotensin converting enzyme inhibitors with diuretics with success. Contrary to some expectations, we find that diuretic therapy poses relatively few problems. It potentiates the effectiveness of most regimens. A review of the liver transplant experience at Mayo Clinic revealed that nearly a third of patients were adequately controlled by either nifedipine or labetalol alone, and an additional third with the addition of a second agent. However, more than 30% of patients found even modest doses of these agents to produce intolerable levels of edema, headache, fatigue, or postural intolerance. These patients changed regimens altogether. This percentage is far higher than essential hypertensive patients managed by the same staff. We attribute this to enhanced sensitivity of the liver transplant recipients to medication effects when added to the considerable burdens of postoperative recovery, resumption of physical activity after prolonged debilitation, and interactions with other medications.

Late Follow-up

The majority of liver transplant patients followed at our institution remain on antihypertensive medications indefinitely. Occasionally, hypertension accelerates at a relatively late stage. This usually coincides with a change in renal function, steroid dose, and sodium retention. As was observed in the patient described in this article, the severity of hypertension may change over time. It may ultimately resolve altogether. The reasons for these changes are not well understood. The reasons for a fall in vascular resistance as illustrated in Table 1 are not clear. However, other forms of CSA toxicity, particularly central nervous system neurotoxicity, have been related to circulating lipoprotein levels. De Groen has offered the hypothesis that cellular toxicity from CSA depends on cell entry, for which it competes at the low-density lipoprotein receptor with low-density lipoprotein itself. Hence, there is an inverse relation between low-density lipoprotein and CSA toxic effects for any given level of circulating CSA. Recovery from liver failure is associated with rising cholesterol, triglyceride, and lipoprotein levels. Perhaps these levels finally limit the entry of CSA into some vascular smooth muscle cells. Such an explanation, however, does not explain the relative lack of such an effect within the kidney, as shown by the patient presented in this article.

Summary

Hypertension develops in most patients after transplantation when immunosuppression is based on cyclosporine and prednisone. The pathogenesis appears to be multifactorial but involves rapidly rising vasoconstrictor tone in renal and systemic vascular beds. Much of this tone reflects abnormal vascular function, characterized by impaired prostacyclin and EDRF effects, in conjunction with increased vasoconstriction due to endothelin and possibly other factors. Effective management of the transplant recipient depends on preventing excessive vasoconstriction, usually with calcium channel blocking agents.

Acknowledgments

These studies were supported by a grant-in-aid from the American Heart Association (91-0127-10) and National Institutes of Health General Clinical Research Center Grant M01-RR-585.

Questions and Answers

Dr Gerald F. DiBona (University of Iowa, Iowa City): I’ve been struck by the influence of cyclosporine not only on peripheral sympathetic nerve activity but the relatively higher incidence of events that suggest central effects, seizures, tremor, and signs of altered mental state. Is FK 506 characterized by these kinds of effects as well?

Dr Textor: It has been. It is interesting to watch the development of the immunosuppression programs, because we really don’t know what the optimal dose of FK 506 is. This was the same situation with cyclosporine initially. The initial trials, which were done mainly in liver transplants, found that the incidence of unacceptable tremors, hallucinations, and a variety of other effects can actually be higher with FK 506, but a much higher dose of FK 506 almost certainly was being used than will be finally needed. As was the case with cyclosporine, the message has been that to reduce toxicity, one has to find a lower dose. And that has happened. Neurotoxicity is a good example of an interesting hypothesis about why these toxicities occur. One of them has been that because of its lipophilic properties, cyclosporine crosses membranes easily. The argument has been that an inverse relation exists between the amount of low-density lipoprotein cholesterol and the incidence of toxicity. In vitro data suggest that cyclosporine competes with the low-density lipoprotein receptor so that as low-density lipoprotein levels change, the incidence of toxicity falls. I think that this is most striking in the liver group, because the liver synthetic dysfunction produces very low levels of cholesterol. Over the course of a year after transplant, a tremendous rise in the level occurs. I think that this has been less obvious in other transplant studies, but it remains an interesting possibility.

Dr Christie Thomas (University of Iowa, Iowa City): What is the mechanism of the escape of hypertension?
Dr Textor: That is an excellent question, and to be honest with you, I do not have an answer. I have to underscore that it is not common. We reviewed closely 278 patients and found 13 in whom antihypertensive medications have later been discontinued, and the patients remained normotensive. The data would indicate that it is not because of a change in renal function. We really don't know the mechanisms affecting the peripheral vessels yet, but I think it is an area that deserves close study.

Dr Annette Fitz (University of Iowa, Iowa City): Early in the course of increased renal resistance after liver transplant, can vasoconstriction be reversed by acetylcholine infusion?

Dr Textor: Good question. I don't know the answer to that. There are some published data that early renal changes are functional. I say that based on the fact that it can be reversed, for example, with dopamine or by withholding cyclosporine. The rule has been that, if at some point you withdraw cyclosporine, most of the vasoconstriction resolves. However, some changes are not reversible. Furthermore, there are some data that calcium channel blockers can interfere with vasoconstriction, but it's been hard to sustain that dilation. There appear to be functional elements that can be manipulated. But whether, for example, the human kidney is sensitive specifically to endothelium-dependent vasodilators, I really don't know.

Charles Pruchno (University of Iowa, Iowa City): Do you see the intense vasoconstriction if CSA is given as a constant infusion? Could the use of frequent small doses in combination with erythromycin, diltiazem, ketoconazole, etc, in clinical settings alleviate CSA-induced vasoconstriction?

Dr Textor: A very practical question about which there are limited data. There have been a few studies in normal volunteers examining the intravenous effect. Acute studies using short-term infusion of cyclosporine for a day or so do in fact identify such renal hemodynamic changes, which have been less dramatic than those observed clinically. In some animal studies, cumulative effects develop with time as well, so we don't know how to interpret short-term studies. But your question as to whether intravenous or constant infusion will avoid these issues really hasn't been addressed. The intense daily changes in kidney perfusion can be prevented. At the American Society of Nephrology meeting in 1992, a study was presented about the use of another dihydropyridine calcium antagonist that was able to prevent the daily renal hemodynamic changes. It did not change any of the hormonal changes such as urinary endothelin; however, it was able to blunt the vasoconstriction.

Dr William Lawton (University of Iowa, Iowa City): Could decreased cardiac output mediate the decreased GFR and renal blood flow in (1) renal transplant studies showing decreased GFR and renal blood flow 6 hours after CSA and (2) liver transplant studies showing chronic decreased GFR and renal blood flow?

Dr Textor: That explanation is unlikely. The data in liver transplant recipients demonstrate very high cardiac outputs before transplant. We have observed that a large part of that resolves to normal levels within the first couple of weeks. It's a little controversial, because some studies indicate that high output may persist in some liver transplant recipients for a longer time. Our view is that on balance the hyperdynamic state resolves eventually. The issue is the time sequence. However, cardiac output falls to basically normal levels, so that a year after transplant the hemodynamic profile is one of enhanced peripheral vascular resistance. That has been consistent with observations of cardiac transplantation groups at Stanford and Pittsburgh using formal repeat catheterization methods. Studies of renal hemodynamics at the same time indicate vasoconstriction everywhere. The volume status of transplant recipients has been a little unclear, but in general, plasma volume measurements indicate that there may be some volume expansion. Altogether, there is little to indicate in humans that the decreased kidney function is related to decreased cardiac output.

Dr J. Andrew Bertolatus (University of Iowa, Iowa City): What dose of cyclosporine (or what cyclosporine blood levels) do you aim for at 6 to 12 months after transplant?

Dr Textor: Target blood levels are about 100 ng/dL during long-term follow-up. The liver transplant situation is especially sensitive to the function of the biliary tract, which may affect absorption of cyclosporine. Hence, the specific dose required to achieve a blood level is highly variable. They typically don't absorb cyclosporine well initially, so people follow blood levels as the hallmark.

Dr Larry Tobacman (University of Iowa, Iowa City): What is known about the expression in endothelial cells of the molecules mediating FK 506 and/or cyclosporine immunosuppressive effects, such as cyclophilin, calcineurin, etc?

Dr Textor: I know of few data on it. I don't know if there are binding sites specifically on endothelial cells. As I'm sure you're aware, many cells are affected and localize cyclosporine, but virtually all membranes are affected. Whether CSA enters through receptors or by alternate internal channels is really not clear.

References


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