Systemic and Renal Effects of Nifedipine in Cyclosporine-Associated Hypertension

Stephen C. Textor, Lora Schwartz, Daniel J. Wilson, Russell Wiesner, Juan C. Romero, Jo Augustine, Paul Kos, Eileen Hay, Gregory Gores, E. Rolland Dickson, Ruud A. Krom, Michael Porayko

Abstract
Cyclosporine induces hypertension and widespread vasoconstriction after transplantation in addition to reducing kidney function. We studied hemodynamic, renal, and hormonal effects of monotherapy with nifedipine XL (n=37) in liver transplant recipients within a year after transplant (median, 4.4 months). Systemic hemodynamics were determined with thoracic electrical bioimpedance. Blood pressure before therapy was 172±4/108±2 mm Hg. Sixty-four percent of recipients achieved blood pressures less than 140/90 mm Hg mediated by a fall in systemic vascular resistance index (2427±245 dyne⋅s⋅cm⁻²⋅m⁻¹ in responders versus 2905±281 in nonresponders, P<.01). Despite the fall in systemic vascular resistance, glomerular filtration rates were not changed during nifedipine therapy, as measured by both creatinine and iodohexate clearances. Urinary prostacyclin (6-ketoprostaglandin F₁α) was suppressed below normal from 2468±323 ng/d before transplant to 1103±99 ng/d (P<.01) after transplant and did not change during nifedipine therapy. Urinary thromboxane B₂ and plasma renin activity also fell after transplant and remained low during nifedipine. These data demonstrate that nifedipine can reverse systemic vasoconstriction associated with hypertension after transplantation. Systemic effects were not transmitted to the kidney sufficiently to improve glomerular filtration rate or reverse hormonal changes within the kidney. Hence, vascular and functional regulation of the kidney was dissociated from the systemic circulation during nifedipine administration after transplantation. (Hypertension. 1994;23[suppl 1]:I-220-I-224.)

Key Words
• cyclosporine • nifedipine • calcium channel blockers • hemodynamics • glomerular filtration rate • epoprostenol

Hypertension develops soon after orthotopic liver transplantation in nearly 80% of patients treated with cyclosporine A (CSA) and prednisone. The mechanisms underlying this disorder remain uncertain, although it is characterized by widespread vasoconstriction affecting systemic and regional vessels, including the kidney. Multiple vasoactive systems are affected, including production of prostaglandins and endothelin and activation of sympathetic adrenergic outflow.

The effects of antihypertensive medications on vascular regulation and kidney function after transplantation have not been clearly established. With the use of CSA, glomerular filtration is universally reduced after transplant. Studies in renal transplant recipients indicate that CSA produces intense renal vasoconstriction and loss of glomerular filtration rate (GFR) after each dose, which is associated with elevated urinary endothelin excretion. Calcium channel blocking agents, particularly dihydropyridines, ameliorate experimental nephrotoxicity from CSA and prevent renal vasoconstriction. They may improve GFR in some clinical settings, but this has not been widely examined in conditions other than renal transplantation.

Previous results demonstrate that renal vasoconstriction after liver transplant in humans, unlike the rat, is associated with reduced vasodilating prostaglandins (prostacyclin). The relative ratio of thromboxane to prostacyclin favors vasoconstriction. We elected to examine monotherapy with nifedipine XL because of its capacity to induce vasodilation and its recognized antihypertensive efficacy. Nifedipine does not alter cyclosporine disposition to a clinically important degree.

Methods
The immunosuppression regimen used immediately after transplantation has been described previously. This consisted of CSA (2 to 3 mg/kg IV as a continuous infusion beginning on the second day after transplant, followed by dosage adjustment to maintain trough blood levels between 250 and 400 mg/dL as measured by whole-blood high-performance liquid chromatography), prednisone, or methylprednisolone (200 mg/d on a tapering schedule over the first month to 20 mg/d) and azathioprine (2 mg/kg per day). On day 10 after transplant, the biliary T-tube was clamped. Thereafter, CSA doses were diminished gradually to maintain blood levels between 150 and 250 ng/dL, depending on clinical and bioyep evaluation.

Outpatient studies for this report were obtained after patients were discharged from hospital care. They were seen several times weekly until 1 month after transplant. Thereafter, patient visits were scheduled regularly at 4 and 12 months after transplant, then yearly or as needed. As part of return visits, patients were evaluated at the cyclosporine hypertension unit, where three sitting and standing blood pressure measurements were obtained by nursing personnel. Body weight, medication doses, and electrolyte values were recorded. Twenty-four-hour urine collections for urinary sodium and creatinine clearance were obtained. Hemodynamic studies were performed as described below. Patients were assigned to initial antihypertensive treatment with nifedipine XL (30 mg). The dose was advanced until either goal pressures were obtained (<140/90 mm Hg) or limiting side effects were encountered. Data for subjects during treatment were taken after patients had been receiving therapy for an interval of no less than 1
week. The procedures for this study were reviewed and approved by the Institutional Review Board of the Mayo Foundation.

Hemodynamic Studies
Arterial blood pressures were recorded by an automated oscillometric sphygmomanometer at 5-minute intervals (Accutorr, Datascope, Paramus, NJ). Cardiac output was determined by measurement of stroke volume by changes in thoracic electrical bioimpedance gated during systole using a commercially available unit (NCCOM-3, BoMed Medical Manufacturing, Inc, Irvine, Calif) as reported previously. Stroke volume and cardiac output measurements using electrical bioimpedance agree closely with thermolumination values under widely varying conditions, including liver transplantation,11,12 This instrument uses surface electrocardiographic electrodes applied at the base of the neck and 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 (Z, ohms). Stroke volume was derived from dZ/dt measured during electrical systole using the formula of Kubicek et al with modifications by Skramek. Thoracic size was estimated using a nomogram based on body weight, height, and sex; a single value was used throughout the study for each patient. The coefficient of variation for repeated determinations of stroke volume using this method was 4.5%. Cardiac output was determined as Stroke Volume x 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+[Systolic−Diastolic Pressure]/3) and cardiac index as MAP/CI x 80 dyne ∙ s ∙ cm−2 ∙ m−2.

Renal and Hormonal Studies
Outpatient measurement of GFR was performed using subcutaneous injection of iothalamate as per the method of Israel et al. Plasma renin activity and urinary excretion of prostacyclin (measured as 6-ketoprostaglandin F1α) and thromboxane (measured as the excretion of thromboxane B2) were determined by radioimmunoassay as previously described. Normal values for these measurements were obtained from subjects free of medical conditions participating in the Rochester Family Heart Study during conditions of high (200 mEq/d) and low (10 mEq/d) sodium intake as reported.

Statistical Methods
Data for each visit were recorded in a computer database constructed using CLININFO. Data are expressed as mean ± SEM unless otherwise indicated. Comparison between treatment categories was undertaken using analysis of variance or non-parametric (Wilcoxon Rank Sum) methods as appropriate.

Results
Mean age of the subjects was 48.4 years (16 to 65 years). Twenty-three were female and 14 were male. The median time after transplant for these studies was 4.4 months. Cyclosporine blood levels and prednisone doses are shown in Table 1. Urinary sodium excretion was 108±14 mEq/d. Arterial pressures rose from low levels before transplant (109±3/62±3 mm Hg) to elevated levels by 4 weeks after transplant (164±3/96±2 mm Hg, P<.01). Blood pressure immediately before antihypertensive therapy was started was 172±4/108±2 mm Hg. Blood pressures for the entire group fell to 138±3/84±2 mm Hg during nifedipine administration. Patients were divided into those whose blood pressures were well controlled (defined as MAP < 107 mm Hg: responders) and those whose MAP remained above 107 mm Hg (nonresponders). Thirty-four percent reached goal pressures (<140/90 mm Hg) with nifedipine alone. The mean nifedipine dose was 36±2 mg/d, indicating that the majority of subjects received 30-mg as opposed to 60-mg doses.

Renal Function and Biochemical Values
GFR values as measured by creatinine clearance fell after transplantation from 82±4 to 57±4 mL/min (P<.01). These changes occurred before initiation of

<p>| TABLE 1. Blood Pressure and Laboratory Values During Nifedipine Monotherapy |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Measurement</th>
<th>Responders (64%)</th>
<th>Nonresponders (36%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>135±3</td>
<td>162±5</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78±2</td>
<td>95±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>97±2</td>
<td>117±3</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>110±5</td>
<td>123±8</td>
</tr>
<tr>
<td>(1.34±0.06 mg/dL)</td>
<td>(1.39±0.09 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, mL/s</td>
<td>0.86±0.08</td>
<td>0.86±0.12</td>
</tr>
<tr>
<td>(53±5 mL/min)</td>
<td>(52±7 mL/min)</td>
<td></td>
</tr>
<tr>
<td>CSA level, ng/dL</td>
<td>156±8</td>
<td>186±26</td>
</tr>
<tr>
<td>Prednisone dose, mg/d</td>
<td>11.5±0.6</td>
<td>12.9±1.0</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; and CSA, cyclosporine A. Responders had a MAP < 107 mm Hg; nonresponders, ≥ 107 mm Hg.
antihypertensive therapy. Laboratory results during nifedipine therapy are shown in Table 1. No further decrement was observed, nor improvement, in subsequent measurements during therapy with nifedipine. Creatinine clearance did not differ between responders and nonresponders (Table 1).

Simultaneous measurements of arterial pressure, SVRI, and GFR in 12 subjects determined by formal iothalamate clearance are shown in Fig 2. Despite systemic vasodilation and a reduction in arterial pressure, no change in GFR was observed during nifedipine therapy.

Urinary prostanooid excretion and plasma renin activity are summarized in Table 2. Urinary thromboxane and plasma renin activity levels were elevated before transplantation compared with healthy subjects. Urinary excretion of the prostacyclin metabolite 6-keto-prostaglandin F₁α was normal before transplant. All of these parameters fell within 4 weeks after transplant before antihypertensive therapy. Urinary excretion of 6-keto-prostaglandin F₁α fell after transplant below that observed in healthy subjects and remained low despite nifedipine administration. Both urinary thromboxane excretion and plasma renin activity were not changed after administration of nifedipine. Responders and nonresponders had similar hormonal values.

Clinical Tolerance to Therapy

Subsequent follow-up of patients treated with nifedipine revealed that although initial blood pressure responses were satisfactory in more than 60% of patients, treatment with a single agent was both effective and tolerated clinically in only 35% of patients. Thirty percent discontinued nifedipine because of limiting side effects. Another third of patients eventually required additional agents to achieve sustained blood pressure control and/or relieve edema.

Discussion

The results of these studies demonstrate that systemic hemodynamic changes during nifedipine administration after liver transplant were independent of changes in glomerular filtration and renal eicosanoid excretion. Hypertension after liver transplantation was treated effectively with nifedipine alone in a large proportion (64%) of patients. Pressure reduction was mediated hemodynamically by a reduction of systemic vascular resistance. Reduction of arterial pressure and systemic vasoconstriction with nifedipine, however, did not translate into improved renal function, nor did it return urinary prostacyclin excretion to normal levels.

Hypertension after transplantation during the cyclosporine era poses a considerable management problem. Failure to recognize and lower blood pressure after transplantation occasionally has led to rapidly progressive and severe manifestations, including intracranial hemorrhage, encephalopathy, microangiopathic hemolysis, and death. The mechanisms underlying this disorder remain uncertain. Hemodynamic studies consistently demonstrate widespread vasoconstriction affecting the kidney and other vascular beds. Many systems regulating local vascular tone are disturbed after transplantation.

In experimental models, CSA stimulates release of the potent vasoconstrictor endothelin. Circulating levels rise transiently after liver transplantation in humans and remain above normal. Unlike animal models, in which eicosanoids rise with CSA exposure, renal production of vasodilating prostaglandins in humans including prostacyclin, derived from vascular endothelium, remains unchanged.

**TABLE 2. Results of Hormonal Measurements**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Pretransplant</th>
<th>Posttransplant Before BP Treatment</th>
<th>Posttransplant Nifedipine Treatment</th>
<th>Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Ketoprostaglandin F₁α ng/d</td>
<td>2468±323</td>
<td>1103±99*†</td>
<td>771±134*</td>
<td>2248±187</td>
</tr>
<tr>
<td>Thromboxane B₂, ng/d</td>
<td>3326±366</td>
<td>1337±178†</td>
<td>1234±151†</td>
<td>1137±154</td>
</tr>
<tr>
<td>Plasma renin activity, (ng/dL)/h</td>
<td>7.8±1.7</td>
<td>1.5±0.6†</td>
<td>1.7±0.26†</td>
<td>1.22±0.45</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SEM.

*P<.01 vs healthy subjects.

†P<.01 vs pretransplant.

**FIG 1.** Bar graphs show systemic hemodynamic measurements in patients treated with nifedipine alone. Responders were defined as patients achieving mean arterial pressures less than 107 mm Hg (dark shaded bars). Cardiac index (Cl) did not change during nifedipine administration. Fall in pressure reflected a fall in systemic vascular resistance index (SVRI). **P<.01.**
Calcium channel blocking agents have been proposed both to augment the immunosuppressive actions of cyclosporine and to limit or reverse its vascular effects.\textsuperscript{20,21} Nifedipine administration was effective in a large portion of our patients in reducing both arterial pressure and systemic resistance. However, our data indicated that nifedipine did not improve renal function in liver transplant recipients during chronic therapy. These results differ from previous studies which suggest that calcium channel blockers lead to improved GFR in experimental CSA nephrotoxicity and after renal transplantation.\textsuperscript{20,22} Our results in liver transplant recipients, whose kidneys are not subject to surgical or preservation injury, are in agreement with studies that have not observed improved filtration.\textsuperscript{23,24}

The present data extend these results to suggest that despite reduction of systemic vasoconstriction, nifedipine did not reverse vasoconstriction within the kidney sufficiently to improve glomerular filtration or change eicosanoid excretion at these doses and under these conditions. Recent studies indicate that temporary, intense daily vasoconstriction in renal allografts with daily CSA doses may be prevented with dihydropyridine calcium blockers\textsuperscript{a} despite elevated urinary excretion of the potent vasoconstrictor endothelin. However, the baseline level of glomerular filtration and renal blood flow, which was reduced after transplant, did not improve. Hence, our results in liver transplant recipients are consistent with this observation. Studies in renal transplant recipients treated with isradipine demonstrate a fall in renal vascular resistance and rising renal blood flows after 2 weeks of therapy.\textsuperscript{24} No change in GFR occurred, despite these changes. Renal blood flow was not measured during nifedipine therapy in the present studies. Other explanations, including preferential efferent arteriolar vasodilation leading to increased total blood flow without a change in GFR, cannot be excluded.

Taken together, results from our studies indicate that mechanisms of vascular and functional regulation within the kidney during CSA administration after liver transplantation are independent of those regulating the systemic vasculature. Studies of vascular regulation after transplantation must recognize the heterogeneity of regional vascular beds.

Acknowledgments
These studies were supported by a Grant-in-Aid from the American Heart Association (No. 91-0127-10), National Institutes of Health General Clinical Research Center Grant MO1-RR-585, and a grant from the Mayo Foundation.

References
3. Moss NG, Powell SL, Falk RJ. Intravenous cyclosporine activates afferent and efferent renal nerves and causes sodium retention in


Systemic and renal effects of nifedipine in cyclosporine-associated hypertension.
S C Textor, L Schwartz, D J Wilson, R Wiesner, J C Romero, J Augustine, P Kos, E Hay, G Gores and E R Dickson

Hypertension. 1994;23:I220
doi: 10.1161/01.HYP.23.1_Suppl.I220

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/23/1_Suppl/I220

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/