Cyclosporine Causes Sympathetically Mediated Elevations in Arterial Pressure in Rats

Barbara J. Morgan, Teresa Lyson, Urs Scherrer, and Ronald G. Victor

Cyclosporine-induced immunosuppression has emerged as a new cause of hypertension, but the underlying mechanisms are poorly understood. In patients, this hypertension is accompanied by sympathetic neural activation. We therefore hypothesized that increased sympathetic nerve discharge is an important mechanism by which cyclosporine raises blood pressure. To test this hypothesis, we examined effects of acute administration of cyclosporine (5 mg/kg i.v.) or vehicle on renal and lumbar sympathetic nerve activity, renal and femoral blood flow velocity (pulsed Doppler flowmetry), and arterial pressure in chloralose-anesthetized rats. Vehicle had no effect on sympathetic nerve activity, whereas cyclosporine caused renal and lumbar sympathetic nerve activity to increase progressively over 60 minutes to levels that were 362 ± 46% and 388 ± 70%, respectively, of the baseline values (p < 0.05). These increases in sympathetic nerve activity were accompanied by proportional increases in renal and femoral vascular resistance and sustained increases in mean arterial pressure (+19 ± 3 mm Hg, p < 0.05 versus baseline). The cyclosporine-induced increases in regional vascular resistance and arterial pressure were greatly attenuated, or abolished, by ganglionic blockade or by clonidine (central sympatholysis) but were unaffected by angiotensin converting enzyme inhibition. These findings demonstrate that in an anesthetized animal preparation, the vasoconstrictor and blood pressure-raising effects of cyclosporine are caused by sympathetic neural activation. (Hypertension 1991;18:458–466)
model that allowed us to examine the importance of sympathetic activation in causing increases in vascular resistance and arterial pressure evoked by acute administration of cyclosporine. We recorded sympathetic discharge and blood flow to both the kidney and the hind limb to test the hypothesis that cyclosporine evokes widespread sympathetic activation producing neurogenic vasoconstriction and elevated arterial pressure.

Methods

General Methods

Experiments were performed on female Sprague-Dawley rats (220–300 g) (Charles River, Kingston, Mass.). Anesthesia was induced with ketamine HCl (80 mg/kg i.m.) and was maintained with alphachloralose (60 mg/kg i.v.). The initial dose of alphachloralose was infused over 20 minutes before the start of the experiments (total volume infused, 0.5–0.7 mL). Anesthesia was supplemented as necessary during the instrumentation period with alphachloralose (10 mg/kg i.v.; total volume infused, 0.1 mL); no additional chloralose was necessary during the experimental protocol. Atropine sulfate (0.5 mg/kg) was given subcutaneously to prevent excessive tracheal secretions. The trachea was cannulated, and the animal was artificially ventilated (Harvard Apparatus, South Natick, Mass.) using room air and supplemental oxygen. A femoral vein was cannulated for administration of drugs. Arterial pressure was monitored via a femoral artery catheter, which was connected to a P23ID pressure transducer (Gould Electronics, Oxnard, Calif.). Heart rate was measured from the arterial pressure signal using a biotachometer (Gould Electronics, Cleveland, Ohio). Arterial blood gases, PaCO₂, and arterial pH were maintained within normal limits. Administration of supplemental oxygen produced mild hyperoxemia (Paco₂=120–130 mm Hg). The urinary bladder was catheterized via the urethra to permit free flow of urine. Core temperature was maintained at 37±1°C with an external heat source.

Recording of Renal and Lumbar Sympathetic Nerve Activity

In each experiment, either lumbar or renal sympathetic nerve activity was recorded. The left kidney was exposed through a retroperitoneal dissection, and we recorded sympathetic nerve activity from the branch of the renal nerve that lies on top of or just to the side of the proximal renal artery near its origin from the aorta. The portion of the lumbar sympathetic chain between the left renal artery and the left iliolumbar artery was exposed through a midline abdominal incision. The nerves were dissected free and affixed to bipolar platinum electrodes using silicone rubber (SilGel 604, Wacker-Chemie, Munich, FRG) according to the technique of Schad and Seller.19 Nerve action potentials were detected by a high impedance probe (model 511, Grass Instruments, Quincy, Mass.) and amplified 20,000-fold by a Grass P511 amplifier with a bandpass filter with a bandwidth of 100–1,000 Hz. For monitoring during the experiment, the filtered neurogram was routed to an oscilloscope (model 511A, Tektronix, Chicago, Ill.) and to an audio amplifier and loudspeaker. For permanent recording and analysis, the filtered neurogram was routed through a nerve traffic analyzer (model 706C, University of Iowa Bioengineering, Iowa City, Iowa) that counted nerve spikes exceeding a threshold voltage set just above the noise level; this threshold voltage and the level of amplification of nerve signals were constant throughout the experimental protocol. During the experiment, output from the spike counter, the arterial pressure transducer, the cardiotorachometer, and the Doppler flowmeter were recorded continuously using a physiological recorder (model 2800S, Gould Electronics, Cleveland, Ohio). The filtered neurogram, arterial pressure signal, and flow velocity signal were recorded on FM tape using a recorder (model PR-500, Ampex, Redwood City, Calif.) for subsequent playback and analysis.

Measurement of Regional Blood Flow Velocity

In each experiment, blood flow velocity was measured in either the left renal or left femoral artery according to the regional sympathetic outflow under investigation (renal blood flow with renal sympathetic nerve activity, femoral blood flow with lumbar sympathetic nerve activity). A Silastic cuff containing a pulsing Doppler flow probe was placed around the artery. Changes in blood flow velocity were measured by recording the mean Doppler shift in kilohertz. For permanent recording and analysis, the Doppler shift was filtered neurogram was routed through a nerve traffic analyzer (model 706C, University of Iowa Bioengineering, Iowa City, Iowa) that counted nerve spikes exceeding a threshold voltage set just above the noise level; this threshold voltage and the level of amplification of nerve signals were constant throughout the experimental protocol. During the experiment, output from the spike counter, the arterial pressure transducer, the cardiotorachometer, and the Doppler flowmeter were recorded continuously using a physiological recorder (model 2800S, Gould Electronics, Cleveland, Ohio). The filtered neurogram, arterial pressure signal, and flow velocity signal were recorded on FM tape using a recorder (model PR-500, Ampex, Redwood City, Calif.) for subsequent playback and analysis.

Experimental Protocols

Protocol 1: Effects of cyclosporine versus vehicle on arterial pressure, heart rate, and renal and lumbar sympathetic nerve activity and renal and femoral vascular resistance. After 20 minutes of stable baseline data collection, cyclosporine (Sandimmune, Sandoz Pharmaceuticals, E. Hanover, N.J.) (n=29 rats) or an equivalent volume of vehicle (Cremophor EL, BASF Aktiengesellschaft, Ludwigshafen, FRG) (n=15 rats) was infused intravenously over 20 minutes to a total dose of 5 mg/kg. This dose of cyclosporine is within the dose range used clinically and has been shown to prolong cardiac allograft survival in the rat.16,20 Arterial pressure, heart rate, and either renal sympathetic nerve activity and renal blood flow velocity or lumbar sympathetic nerve activity and femoral blood flow velocity were measured continuously before, during, and for 1 hour after the infusion. In more than one half of these experiments, we extended data collection for up to 2 hours after infusion of cyclosporine or vehicle.
To determine if the sympathetic effect of cyclosporine is dose-dependent, we recorded in 17 additional experiments renal sympathetic nerve activity and arterial pressure for 1 hour after intravenous infusion of only 0.5 mg/kg cyclosporine, which is one tenth of the dose used in the rest of our experiments.

To examine the importance of activation of the sympathetic system and of the renin-angiotensin system in causing the hemodynamic responses to cyclosporine, we performed several additional protocols (No. 2–4) in which we treated several groups of rats with different pharmacological blocking agents before the administration of cyclosporine. The experiments in protocol 1 serve as the controls for these additional experiments. We were unable to study responses to repeated infusions of cyclosporine in the same rat because sympathetic nerve activity never returned to baseline once cyclosporine was administered.

**Protocol 2: Hemodynamic responses to cyclosporine in rats pretreated with ganglionic blockade (n=14).** Chlorisondamine (5 mg/kg i.v.) (CIBA-GEIGY, Suffern, N.Y.) was given to block ganglionic transmission irreversibly before administration of cyclosporine. The aim of this protocol was to examine effects of cyclosporine alone, without sympathetic activation, on regional vascular resistance and arterial pressure. In every experiment, the efficacy of ganglionic blockade was demonstrated by the complete cessation of postganglionic renal sympathetic nerve activity. After 20 minutes of stable baseline data collection, cyclosporine (5 mg/kg) was infused intravenously over a 20-minute period. Arterial pressure, heart rate, renal sympathetic nerve activity, and renal or femoral blood flow velocity were recorded continuously before, during, and for 1 hour after the infusion of cyclosporine.

To determine if ganglionic blockade would reverse as well as prevent the pressor response to cyclosporine, we administered chlorisondamine in 10 of the rats studied in protocol 1 2 hours after (rather than before) infusion of cyclosporine (n=6) or vehicle (n=4).

**Protocol 3: Hemodynamic responses to cyclosporine in rats pretreated with clonidine (n=15).** To determine if the effects of chlorisondamine on hemodynamic responses to cyclosporine were caused specifically by interruption of sympathetic outflow rather than by some nonspecific property of this agent, we performed additional experiments in which cyclosporine-induced sympathetic activation was totally prevented by clonidine (a central sympatholytic agent) rather than by ganglionic blockade. Clonidine hydrochloride (10 µg/kg i.v.) (Boehringer Ingelheim, Ridgefield, Conn.) was given before administration of cyclosporine. In each experiment, central sympathetic inhibition was documented by the complete cessation of renal or lumbar sympathetic nerve activity. After 20 minutes of stable baseline data collection, cyclosporine (5 mg/kg) was infused intravenously over a 20-minute period. Arterial pressure, heart rate, renal or lumbar sympathetic nerve activity, and renal or femoral blood flow velocity were recorded continuously before, during, and for 1 hour after infusion of cyclosporine.

In all, we studied a total of 101 rats: 61 rats in protocol 1, 14 rats in protocol 2, 15 rats in protocol 3, and 11 rats in protocol 4. All procedures followed were in accordance with the guidelines set up by the Institutional Review Board for Animal Research at the University of Texas Southwestern Medical Center.

**Data Analysis**

Repeated-measures analyses of variance with Dunnett post hoc tests were used to compare the responses to cyclosporine or vehicle with the baseline values and to examine effects of pharmacological blocking agents on the responses to cyclosporine. Paired t tests were used to examine effects of pharmacological blocking agents on baseline hemodynamic measurements. Unpaired t tests were used to compare baseline values between groups and unpaired t tests with Bonferroni adjustments for multiple comparisons were used to compare between-group differences in the responses to each intervention at a given point in time. Values of p<0.05 were considered statistically significant. In the text and tables, data are expressed as mean±SEM.

**Results**

Intravenous infusion of cyclosporine produced long-lasting and dose-dependent increases in sympathetic activity and arterial pressure (Table 1 and Figures 1–3). In contrast, intravenous infusion of vehicle had no effect on sympathetic nerve activity and caused only a small and very transient increase in arterial pressure (Table 2). By 1 hour after infusion...
Table 1. Effects of Cyclosporine (5 mg/kg i.v.) on Arterial Pressure, Heart Rate, Sympathetic Nerve Activity, and Regional Vascular Resistance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Minutes during cyclosporine infusion</th>
<th>Minutes after cyclosporine infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>84±2</td>
<td>108±2* 116±2* 113±2* 109±3* 107±3* 107±3*</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>47±2</td>
<td>51±2* 53±2* 55±2* 54±2* 54±2* 54±2*</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>341±6</td>
<td>360±6* 367±5* 359±6* 359±6* 360±6* 363±5*</td>
<td></td>
</tr>
<tr>
<td>Renal sympathetic nerve activity (%)</td>
<td>100</td>
<td>210±19* 289±36* 304±40* 328±40* 363±48* 362±46*</td>
<td></td>
</tr>
<tr>
<td>Renal vascular resistance (%)</td>
<td>100</td>
<td>131±5* 140±7* 129±4* 128±5* 126±5* 122±6*</td>
<td></td>
</tr>
<tr>
<td>Lumbar sympathetic nerve activity (%)</td>
<td>100</td>
<td>146±36 155±32 201±39* 257±41* 325±61* 388±70*</td>
<td></td>
</tr>
<tr>
<td>Femoral vascular resistance (%)</td>
<td>100</td>
<td>109±3* 109±4* 115±5* 125±8* 131±7* 140±7*</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM for 29 rats. Renal sympathetic nerve activity and renal vascular resistance data are taken from 15 rats. Lumbar sympathetic nerve activity and femoral vascular resistance data are taken from 14 rats.

*p<0.05 vs. baseline value.

†p<0.05 rats given cyclosporine vs. rats given vehicle.

of cyclosporine, renal sympathetic nerve activity had increased to values that were 171±21% and to 362±46% of baseline with 0.5 mg/kg and with 5 mg/kg doses, respectively (p<0.05 versus baseline), and mean arterial pressure had increased by +7±2 and by +23±2 mm Hg, respectively.

Table 1 and Figures 1 and 2 depict the time course of the arterial pressure and regional sympathetic and vascular responses during and after infusion of the 5 mg/kg dose of cyclosporine. Renal sympathetic nerve activity, renal vascular resistance, and arterial pressure all increased rapidly during the infusion of cyclosporine, renal sympathetic nerve activity had increased to values that were 171±21% and to 362±46% of baseline with 0.5 mg/kg and with 5 mg/kg doses, respectively (p<0.05 versus baseline), and mean arterial pressure had increased by +7±2 and by +23±2 mm Hg, respectively.

Figure 1. Illustrative recordings from two separate experiments in which cyclosporine (CsA) was infused intravenously over 20 minutes to a total dose of 5 mg/kg. Arterial pressure was measured in both experiments. Panel A: Effects of CsA on renal blood flow velocity and renal sympathetic nerve activity (SNA), the latter displayed as a time-frequency histogram. Panel B: Effects of CsA on femoral blood flow velocity and lumbar SNA. Infusion of CsA produced a rapid increase in arterial pressure that was maintained for hours after the infusion. This increase in arterial pressure was accompanied by a parallel increase in renal SNA (panel A) and a more gradual increase in lumbar SNA (panel B). Despite the increase in blood pressure, regional blood flow velocities did not increase but rather tended to decrease, indicating vasoconstriction in both beds.
Hypertension Vol 18, No 4 October 1991

Mean Arterial Pressure (mmHg)

Renal Vascular Resistance (mmHg/kHz)

Femoral Vascular Resistance (mmHg/kHz)

Figure 2. Line graphs show summary data of mean arterial pressure, renal vascular resistance (RVR) and renal sympathetic nerve activity (SNA), and femoral vascular resistance (FVR) and lumbar SNA at baseline, during infusion of cyclosporine (CsA), and 20, 40, and 60 minutes after the infusion. Data are mean±SEM for 14 rats with measurements of renal SNA and RVR and for 15 rats with measurements of lumbar SNA and femoral vascular resistance. Values for arterial pressure represent the mean data from all 29 rats. *p<0.05 vs. baseline value. CsA produced parallel increases in SNA and vascular resistance in both the hind limb and kidney and sustained increases in arterial pressure.

cyclosporine with the peak increases occurring approximately 10 minutes after the onset of infusion. Renal sympathetic nerve activity, renal vascular resistance, and arterial pressure remained stably elevated for the remainder of the infusion and post-infusion observation period. Although lumbar sympathetic nerve activity and femoral vascular resistance also increased substantially with cyclosporine, the temporal pattern of these responses was slow and progressive in contrast to the rapid and sustained increase in renal sympathetic nerve activity and vascular resistance. Thus, the initiation of the cyclosporine-induced pressor response closely paralleled the development of the sympathetic and vasoconstrictor response in the kidney but not in the hind limb. In the subset of experiments in which observations were continued for 2 hours after cyclosporine infusion, the increases in mean arterial pressure (+19±3 versus +17±3 mm Hg, first versus second hour) and in renal sympathetic nerve activity (362±46% versus 492±91% of baseline, first versus second hour) remained stable during this extended period of observation while lumbar sympathetic nerve activity continued to increase progressively over the entire 2-hour period (388±70% versus 545±82% of baseline, p<0.05 first versus second hour).

The effects of chlorisondamine (ganglionic blockade), clonidine (central sympatholysis), and enalapril (angiotensin converting enzyme inhibition) on baseline hemodynamic measurements and the effects of these agents on the responses to cyclosporine are shown in Tables 3–5 and Figure 3. The cyclosporine-induced increases in renal and femoral vascular resistance and in arterial pressure were greatly attenuated or abolished by pretreatment with ganglionic blockade or with clonidine but were unaffected by pretreatment with converting enzyme inhibition (Tables 3–5 and Figure 3). In addition, cyclosporine-induced increases in arterial pressure were reversed when ganglionic blockade was administered 2 hours after infusion of cyclosporine: ganglionic blockade decreased mean arterial pressure from 103±5 to 65±7 mm Hg in rats given cyclosporine and from 82±3 to 66±5 mm Hg in rats given vehicle (p>0.10, mean arterial pressure after ganglionic blockade in cyclosporine-treated versus vehicle rats).

Discussion

Recent neurophysiological studies in patients treated with cyclosporine have prompted the hypothesis that the blood pressure-raising effect of this immunosuppressive agent may be caused in part by activation of the sympathetic nervous system. To test this hypothesis, we performed complementary neurophysiological experiments in rats. The major new findings of this study are twofold. First, cyclosporine causes sustained increases in sympathetic outflow to the kidney and hind limb and corresponding elevations in regional vascular resistance and arterial pressure. Second, these cyclosporine-induced elevations in vascular resistance and arterial pressure are greatly attenuated or abolished when sympathetic discharge is eliminated by either ganglionic blockade or clonidine. In contrast, the increases in vascular resistance and arterial pressure were unaffected by converting enzyme inhibition. These findings demonstrate that in an anesthetized animal preparation, the vasoconstrictor and blood pressure-raising effects of
cyclosporine are caused mainly by sympathetic neural activation. Although this interpretation is based on acute administration of cyclosporine to rats, there are some important similarities between the neurocirculatory responses observed in the present experiments with those observed in the clinical setting. First, our studies demonstrate that cyclosporine increases sympathetic outflow to the hind limb in rats as well as in humans. Previous studies in both animals and humans have demonstrated that cyclosporine administration has little or no effect on cardiac output and raises arterial pressure by causing vasoconstriction. Although we did not measure cardiac output in our experiments, we found that cyclosporine caused only small increases in heart rate but large increases in vascular resistance in both the kidney and the hind limb. Based on data derived from cell culture and from isolated vascular ring preparations, several nonneurogenic mechanisms have been implicated in the pathogenesis of cyclosporine-induced vasoconstriction. These include 1) a relative increase in the release of vasoconstrictor to vasodilator prostaglandins, 2) a direct excitatory effect of cyclosporine on vascular smooth muscle, and 3) an augmentation of cellular uptake of calcium and of calcium-dependent vasoconstrictor responses to exogenously administered vasoconstrictor substances such as angiotensin II. However, our findings in a whole animal preparation demonstrate that without sympathetic activation, cyclosporine alone has no direct effects on blood pressure. Our data demonstrate that, when cyclosporine is administered to rats anesthetized with alpha-chloralose, arterial pressure consistently remains elevated for hours after a single dose.

Previous studies in both animals and humans have demonstrated that cyclosporine administration has little or no effect on cardiac output and raises arterial pressure by causing vasoconstriction. Although we did not measure cardiac output in our experiments, we found that cyclosporine caused only small increases in heart rate but large increases in vascular resistance in both the kidney and the hind limb. Based on data derived from cell culture and from isolated vascular ring preparations, several nonneurogenic mechanisms have been implicated in the pathogenesis of cyclosporine-induced vasoconstriction. These include 1) a relative increase in the release of vasoconstrictor to vasodilator prostaglandins, 2) a direct excitatory effect of cyclosporine on vascular smooth muscle, and 3) an augmentation of cellular uptake of calcium and of calcium-dependent vasoconstrictor responses to exogenously administered vasoconstrictor substances such as angiotensin II. However, our findings in a whole animal preparation demonstrate that without sympathetic activation, cyclosporine alone has no direct effects on blood pressure. Our data demonstrate that, when cyclosporine is administered to rats anesthetized with alpha-chloralose, arterial pressure consistently remains elevated for hours after a single dose.

Previous studies in both animals and humans have demonstrated that cyclosporine administration has little or no effect on cardiac output and raises arterial pressure by causing vasoconstriction. Although we did not measure cardiac output in our experiments, we found that cyclosporine caused only small increases in heart rate but large increases in vascular resistance in both the kidney and the hind limb. Based on data derived from cell culture and from isolated vascular ring preparations, several nonneurogenic mechanisms have been implicated in the pathogenesis of cyclosporine-induced vasoconstriction. These include 1) a relative increase in the release of vasoconstrictor to vasodilator prostaglandins, 2) a direct excitatory effect of cyclosporine on vascular smooth muscle, and 3) an augmentation of cellular uptake of calcium and of calcium-dependent vasoconstrictor responses to exogenously administered vasoconstrictor substances such as angiotensin II. However, our findings in a whole animal preparation demonstrate that without sympathetic activation, cyclosporine alone has no direct effects on blood pressure. Our data demonstrate that, when cyclosporine is administered to rats anesthetized with alpha-chloralose, arterial pressure consistently remains elevated for hours after a single dose.

### Table 2. Effects of Vehicle on Arterial Pressure, Heart Rate, Sympathetic Nerve Activity, and Regional Vascular Resistance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>Minutes after vehicle infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88±3</td>
<td>93±4</td>
<td>95±4*</td>
<td>94±4</td>
<td>89±4</td>
<td>87±3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>341±6</td>
<td>340±6</td>
<td>341±6</td>
<td>341±6</td>
<td>341±6</td>
<td>342±7</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>49±2</td>
<td>49±2</td>
<td>50±2</td>
<td>50±2</td>
<td>51±3</td>
<td>47±2</td>
</tr>
<tr>
<td>Renal sympathetic nerve activity (%)</td>
<td>100</td>
<td>95±4</td>
<td>93±6</td>
<td>92±8</td>
<td>83±13</td>
<td>102±20</td>
</tr>
<tr>
<td>Renal vascular resistance (%)</td>
<td>100</td>
<td>101±2</td>
<td>102±3</td>
<td>103±4</td>
<td>102±6</td>
<td>101±2</td>
</tr>
<tr>
<td>Lumbar sympathetic nerve activity (%)</td>
<td>100</td>
<td>86±11</td>
<td>92±8</td>
<td>106±6</td>
<td>102±27</td>
<td>108±11</td>
</tr>
<tr>
<td>Femoral vascular resistance (%)</td>
<td>100</td>
<td>97±6</td>
<td>97±6</td>
<td>97±11</td>
<td>101±5</td>
<td>98±6</td>
</tr>
</tbody>
</table>

* Values are mean±SEM for 15 rats. Renal sympathetic nerve activity and renal vascular resistance data are from 10 rats. Lumbar sympathetic nerve activity and femoral vascular resistance data are from five rats. *p<0.05 vs. baseline value.
TABLE 3. Hemodynamic Responses to Cyclosporine After Ganglionic Blockade

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline before ganglionic blockade</th>
<th>Baseline after ganglionic blockade</th>
<th>Minutes after infusion of cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91±4</td>
<td>69±3*</td>
<td>79±4†</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>53±3</td>
<td>40±2*</td>
<td>43±2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>341±9</td>
<td>329±9</td>
<td>330±9</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg/kHz)</td>
<td>47±9</td>
<td>33±8</td>
<td>30±7</td>
</tr>
<tr>
<td>Femoral vascular resistance (mm Hg/kHz)</td>
<td>141±11</td>
<td>52±4*</td>
<td>50±4</td>
</tr>
</tbody>
</table>

Values are mean±SEM for 14 rats.

*p<0.05 significant effect of ganglionic blockade on baseline values.

Cyclosporine also has been shown to augment the contractile response of isolated blood vessels to a given level of sympathetic nerve stimulation. Thus, the increased vasomotor tone observed during administration of cyclosporine to intact animals and humans may result from the combination of both augmented neuroeffector mechanisms and augmented levels of central sympathetic outflow.

Previous studies in rats have shown that large doses of cyclosporine increase renal sympathetic outflow and renal vascular resistance. Our present findings confirm those observations and extend them in several ways. First, the previous work suggested that the vasoconstrictor effects of cyclosporine are restricted to the kidney and have little, if any, effect on systemic vascular resistance and arterial pressure. In contrast, our data demonstrate that cyclosporine causes sympathetic activation and vasoconstriction in the hind limb as well as the kidney and that this widespread sympathetic activation produces sustained elevations in arterial pressure.

In our study the percentage increases in renal sympathetic nerve activity caused by cyclosporine are more than five times larger than those reported previously, despite a 50% lower dose of cyclosporine used in our study (5 versus 10 mg/kg). We suggest that the much larger increases in sympathetic activity and in arterial pressure observed in our study are related in part to the use of chloralose anesthesia, which causes less depression of autonomic reflexes than the barbiturate anesthesia used in the previous study. Third, our additional finding that cyclosporine increases sympathetic discharge even with a very low dose (0.5 mg/kg i.v.) suggests that sympathetic activation is not merely a neurotoxic response to cyclosporine overdose but rather is a predictable, dose-dependent response to cyclosporine.

The temporal association between the rapid increase in arterial pressure and in renal sympathetic nerve activity and vascular resistance and their temporal dissociation from the slower increase in lumbar sympathetic nerve activity and femoral resistance suggest two important points: 1) the cyclosporine-induced pressor response may be initiated by renal vasoconstriction but maintained by vasoconstriction in the hind limb as well as the kidney and 2) the increases in renal and lumbar sympathetic nerve activity are likely to be governed by different mechanisms. Because cyclosporine has been shown to stimulate chemosensitive renal afferents in rats, we

TABLE 4. Hemodynamic Responses to Cyclosporine After Clonidine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline before clonidine</th>
<th>Baseline after clonidine</th>
<th>Minutes after infusion of cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91±4</td>
<td>74±3*</td>
<td>81±3†</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>52±2</td>
<td>45±2*</td>
<td>44±2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>323±7</td>
<td>312±12</td>
<td>305±12</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg/kHz)</td>
<td>30±8</td>
<td>24±6</td>
<td>22±5</td>
</tr>
<tr>
<td>Femoral vascular resistance (mm Hg/kHz)</td>
<td>129±12</td>
<td>73±8*</td>
<td>78±11</td>
</tr>
</tbody>
</table>

Values are mean±SEM for 15 rats.

*p<0.05 significant effect of clonidine on baseline values.

fp<0.05 cyclosporine vs. baseline after clonidine.
speculate that a local renorenal reflex may initiate the rapid increase in renal sympathetic nerve activity. Because cyclosporine has been shown to cross the blood–brain barrier and produce central nervous system toxicity in patients,23,46 we speculate that a central neural mechanism may contribute to the slow and progressive increase in lumbar sympathetic nerve activity.

In conclusion, the present data demonstrate that in chloralose-anesthetized rats, sympathetic neural activation is the primary mechanism by which acute administration of cyclosporine causes vasoconstriction and raises arterial pressure. These experimental findings are most directly applicable to the clinical syndrome of acute hypertension during the initiation of cyclosporine therapy but also are consistent with the recent finding that in patients, chronic cyclosporine-induced hypertension is accompanied by chronic sympathetic overactivity.

Acknowledgments

We gratefully acknowledge the research assistance of Chi-Na Kim, LeAnn Ermel, and Troy Obregon. We are indebted to Jere H. Mitchell, MD, for his continued support and critical review of our work; to Patricia Powell for expert assistance in the preparation of the manuscript; to Donald A. Morgan and Ulla C. Kopp, PhD, who served as consultants on this project; to Sandoz Pharmaceuticals Corporation for providing cyclosporine and vehicle; to CIBA-GEIGY Corporation for providing chlorisondamine; and to Boehringer Ingelheim Pharmaceuticals for providing clonidine.

References


---

### Table 5. Hemodynamic and Renal Sympathetic Nerve Responses to Cyclosporine After Converting Enzyme Inhibition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline before enalapril</th>
<th>Baseline after enalapril</th>
<th>Minutes after infusion of cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SEM</td>
<td>Mean±SEM</td>
<td>0</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>101±5</td>
<td>74±5*</td>
<td>103±7†</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>53±3</td>
<td>49±3</td>
<td>54±3†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>355±12</td>
<td>342±5</td>
<td>382±10†</td>
</tr>
<tr>
<td>Renal sympathetic nerve activity (%)</td>
<td>100</td>
<td>139±22*</td>
<td>310±50†</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg/kHz)</td>
<td>40±4</td>
<td>27±3*</td>
<td>32±4†</td>
</tr>
<tr>
<td>Femoral vascular resistance (mm Hg/kHz)</td>
<td>136±12</td>
<td>195±49</td>
<td>265±56†</td>
</tr>
</tbody>
</table>

Mean±SEM for 11 rats. Renal sympathetic nerve activity is expressed as a percentage of the baseline value before converting enzyme inhibition. *p<0.05 significant effect of converting enzyme inhibition on baseline values. †p<0.05 cyclosporine vs. baseline after converting enzyme inhibition.


KEY WORDS • cyclosporine • sympathetic nervous system • secondary hypertension • blood pressure • rat studies
Cyclosporine causes sympathetically mediated elevations in arterial pressure in rats.
B J Morgan, T Lyson, U Scherrer and R G Victor

Hypertension. 1991;18:458-466
doi: 10.1161/01.HYP.18.4.458

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 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/18/4/458

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/