Cyclosporine Therapy After Cardiac Transplantation Causes Hypertension and Renal Vasoconstriction Without Sympathetic Activation

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Background. Hypertension frequently complicates the use of cyclosporine A (CyA) therapy, and it has been suggested that sympathoexcitation may be the underlying mechanism in this form of hypertension.

Methods and Results. To further investigate the possibility of a neurogenic mechanism for this hypertensive effect, we studied the effects of CyA on renal blood flow (n=11), forearm blood flow (n=8), and sympathetic nervous system activity, assessed by renal and whole-body radiolabeled norepinephrine plasma kinetics and muscle sympathetic nerve firing (using microneurography) in cardiac transplant recipients receiving CyA and a reference group of healthy age-matched control subjects (n=17). In 11 cardiac transplant patients (2 hours after cyclosporine dose), renal blood flow was significantly lower than that in 8 control subjects (680±88 vs 1285±58 mL/min, P<.001). In 5 of these transplant patients, renal blood flow was measured before and for 2 hours after oral cyclosporine and fell progressively over this period, by 37% (P<.01). Total body and renal norepinephrine spillover rates in transplant patients were similar to those in control subjects (3070±538 vs 2618±313 pmol/min and 579±124 vs 573±95 pmol/min, respectively), and there was no progressive effect in the 2 hours after cyclosporine dosing. Forearm blood flow was increased 2 hours after CyA administration (1.74±0.31 to 3.12±0.50 mL·100 mL⁻¹·min⁻¹, P<.001), whereas mean arterial blood pressure and noninvasively determined cardiac output (indirect Fick method) were unchanged. Muscle sympathetic nerve discharge rates recorded in 6 of these transplant patients were not different from those in 9 healthy control subjects (37.9±1.0 vs 41.3±2.3 bursts per 100 beats per minute). During 90 to 120 minutes of recording after cyclosporine dosing, nerve firing rates remained unchanged.

Conclusions. CyA therapy causes acute renal vasoconstriction without accompanying systemic hemodynamic effects. These renal effects are nonneural, not being attributable to sympathoexcitation. (Circulation. 1993;88:1101-1109.)

KEY WORDS • hypertension • nervous system • cyclosporine • vasoconstriction

The use of cyclosporine as an immunosuppressive agent in solid organ and bone marrow transplantation has been associated with a significant improvement in graft and patient survival. However, the introduction of cyclosporine has been associated with a significant increase in the incidence of posttransplant hypertension irrespective of the transplanted organ. Hypertension also occurs in patients who have not received transplants but are receiving cyclosporine for other clinical conditions thought to be immunologically mediated.

Several pathophysiological mechanisms have been proposed to explain the hypertensive effect of cyclosporine, including direct and sympathetically mediated vasoconstriction. Some authors have speculated that renal vasoconstriction, with resultant extracellular volume expansion caused by retention of salt and water, provides the probable hypertensive mechanism. The genesis of the renal vasoconstriction remains as yet unclear, but cyclosporine has been shown to possess intrinsic vasoconstrictor properties and also to increase sensitivity to a number of vasoconstrictor substances in isolated blood vessels. Renal sympathoexcitation has been described in animals after acute infusions of cyclosporine. Recently, Scherrer et al measured muscle sympathetic nerve traffic in cardiac transplant recipients and patients with myasthenia gravis who were treated with cyclosporine. They found that sympathetic nerve firing was increased, leading the authors to conclude that cyclosporine-induced hypertension was mediated via the sympathetic nervous system. Conversely, Floras et al described the normalization of muscle sympathetic nerve activity in a patient with hepatic cirrhosis after liver transplantation who was receiving cyclosporine therapy.

The aim of our study, therefore, was to further evaluate a potential direct role for the sympathetic nervous system in the pathogenesis of cyclosporine-induced hypertension in cardiac transplant recipients. Two complementary methods of assessing the activity of the sympathetic nervous system were used: a biochemical technique for measuring sympathetic neurotrans-
mitter overflow to plasma and an electrophysiological technique for determining multiunit sympathetic nerve firing in skeletal muscle. These measurements were performed in conjunction with a hemodynamic evaluation of the influence of cyclosporine on regional (renal and forearm) and total vascular resistance.

Methods

Experimental Subjects

Subjects comprised 20 cardiac transplant recipients (described in the Table) and 17 healthy control subjects. The mean age of the heart transplant recipients was 53 ± 2 years, and the controls were aged 46 ± 3 years. The transplant recipients were a mean of 49 ± 2 weeks after transplant (range, 5 to 124 weeks). At the time of study, all transplant recipients were free from allograft rejection and symptoms of heart failure. They were selected consecutively, independent of their blood pressure status. All subjects were in sinus rhythm during their procedures, confirmed by continuous ECG monitoring in both study protocols. In transplant recipients receiving antihypertensive therapy (see the Table), these medications (including diuretics) were withheld for 72 hours before study. Prednisolone (mean dose, 11.5 ± 0.9 mg/d) and azathioprine (mean dose, 90 ± 10 mg/d) were continued during this period. The healthy control subjects were recruited from the general community by advertisement and underwent thorough medical screening before participation. None of the control subjects were receiving any medications. Tea, coffee, and cigarettes were withheld for a minimum of 12 hours before testing in both transplant recipients and control subjects. Studies were performed in the morning after a standardized light breakfast.

All subjects gave written informed consent, and the study was approved by the Alfred Hospital Ethics Review Committee.

General Study Design

To investigate the potential influence of cyclosporine on the sympathetic nervous system, the study incorporated a biochemical assessment of whole-body and renal sympathetic function together with microneurography to test muscle sympathetic nerve activity. The effects of cyclosporine on hemodynamic variables (blood pressure, cardiac output, renal blood flow, and forearm blood flow) were also determined. These measurements were performed either as single observations (2 hours after dosing) or as multiple observations before and after cyclosporine dosing. When the effects of cyclosporine dosing were examined, transplant recipients received their usual cyclosporine dose (Table) determined previously by the Heart Replacement Service, Alfred Hospital, according to their usual clinical and biochemical protocol. Control subjects did not receive cyclosporine.

Experimental Procedures

Total and renal norepinephrine kinetics and renal blood flow. Measurement of whole-body and renal norepinephrine kinetics and renal blood flow was performed in 14 transplant recipients and 8 control subjects. Under local anesthetic, the brachial or radial artery was cannulated (3.0F, 5-cm catheter, Cook, Brisbane, Australia) for blood pressure monitoring and arterial blood sampling. Infusions of a tracer dose of tritiated norepi-
nephrine (0.7 μCi/min of levo[7-3H] norepinephrine per minute; specific activity, 12 to 20 Ci/mmol; New England Nuclear, Boston, Mass) and para-aminohippuric acid (PAH, Merck Sharp and Dohme, West Point, Pa) were administered via a vein in the left forearm for 60 minutes to achieve steady-state concentrations in plasma. A Courmand catheter (Cook) was advanced to the right renal vein under fluoroscopy. After a further period of rest for 15 minutes in the supine position, simultaneous arterial and renal venous samples were drawn for the determination of plasma catecholamine levels, PAH concentration, and plasma renin activity. Arterial samples were also drawn for determination of the hematocrit and the whole-blood cyclosporine level.

In five of the transplant recipients, hemodynamic measurements were made and arterial and renal venous samples were obtained both before their usual oral dose of cyclosporine and thereafter at 30-minute intervals for 2 hours, whereas in an additional three patients, the same protocol was followed without cyclosporine dosing, these patients serving as a control group for any random effects with time. In the six remaining transplant recipients, single observations were performed only at 2 hours after cyclosporine dosing. Study durations were restricted to a maximum observation period of 2 hours after cyclosporine dosing for the purposes of subject comfort and because of pharmacokinetic data that suggest that whole-blood levels of cyclosporine reach their peak approximately 2 hours after oral administration in cardiac transplant recipients. Control subjects underwent arterial and renal venous sampling at only one time point.

The whole-body spillover rate of norepinephrine was calculated by the isotope dilution method developed in our laboratory. The spillover rate (plasma appearance rate) of norepinephrine is equivalent to the rate of infusion of tritiated norepinephrine (expressed as disintegrations per minute) divided by the specific activity of plasma norepinephrine (disintegrations per minute per picomole). Renal norepinephrine spillover rate was calculated according to the equation

Renal Norepinephrine Spillover Rate = 

\[
\frac{[(Cv-Ca)+(Ca \times ER)] \times PF}{}\]

where Ca and Cv are the arterial and venous plasma concentrations of norepinephrine, respectively, ER is the fractional extraction of norepinephrine tracer across the kidney, and PF is the renal plasma flow (determined from the clearance and fractional renal extraction of PAH). Arterial levels of tritiated dihydroxyphenylglycol (3H-DHPG) were also determined. DHPG is the major intraneuronal metabolite of norepinephrine, and the level of 3H-DHPG is a reflection of the activity of the process for the reuptake of neuronally released norepinephrine. The renal production of 3H-DHPG was determined as the product of the renal blood flow and the renal 3H-DHPG venoarterial difference.

Renal plasma flow was estimated from the whole-body clearance and renal extraction of PAH. The concentration of PAH in arterial and renal venous plasma was determined from standard optical density/PAH concentration curves for each individual's plasma. The renal plasma flow was calculated by correcting the PAH clearance for the renal extraction of PAH. Renal plasma flow was converted to renal blood flow with the use of each subject's hematocrit. The renal vascular resistance was subsequently derived as the ratio of the mean arterial pressure to the renal blood flow.

Arterial and venous blood were also drawn for the determination of plasma renin activity. The renal secretion of renin was then calculated as the product of the renal plasma flow and the venoarterial difference in plasma renin activity.

Microneurography. Efferent sympathetic nerve activity in the peroneal nerve was recorded according to the technique of Valbo et al and as previously performed in our laboratory in six cardiac transplant recipients and nine control subjects. Two of these subjects (patients 15 and 16, Table) also participated in the protocol described above, although the two studies were separated by an interval of at least 2 months.

A sterile tungsten microelectrode with a noninsulated tip 1 mm in diameter (Titronics Medical Instruments, Iowa City, Iowa) was inserted percutaneously into the peroneal nerve, located posterior to the fibular head. A reference electrode was placed subcutaneously in close proximity. Stimuli were delivered through the recording electrode with positioning such that muscle twitches in the peroneal nerve distribution were obtained at <0.6 V. Further careful manipulation of the electrode with afferent testing ensured an optimal site for recording postganglionic sympathetic nerve activity. Raw action potentials were amplified (90 000 to 99 000 times), filtered (700- to 2000-Hz bandwidth), and integrated by use of the 662C-3 Nerve Traffic Analysis System (Bioengineering Department, University of Iowa) to obtain a mean voltage neurogram. Pulse synchronicity and low signal-to-noise ratio confirmed burst activity as being of muscle sympathetic efferent origin. The mean voltage neurogram was recorded on a Gould 2800 multichannel recorder for subsequent manual analysis of burst frequency (expressed as bursts per minute and bursts per 100 beats). Observations in the control subjects were performed at only one time period after 30 minutes of rest in the supine position. In the transplant recipients, recordings were performed before their usual oral dose of cyclosporine (after 30 minutes of supine rest) and at 30-minute intervals after dosing for 90 minutes. In three transplant recipients, recordings were continued for 120 minutes.

Forearm blood flow and cardiac output. Eight cardiac transplant recipients were studied under this protocol (in six of these patients, microneurography was also performed at the same time, as described above). Blood pressure, forearm blood flow, and microneurographic measurements were recorded after a period of 30 minutes of rest, and after cyclosporine administration they were recorded at half-hour intervals for 2 hours. Cardiac output (as described below) and whole-blood cyclosporine levels were determined before and then at hourly intervals after cyclosporine dosing for 2 hours.

Blood pressure was measured noninvasively in these subjects by either a digital volume-clamp method (Finapress; Ohmehda, Denver, Colo) or an oscillometric cuff method (model 9300, Paramed, Calif). Heart rate was monitored electrocardiographically. The cardiac output was determined noninvasively by the indirect Fick technique with a commercially available respiratory gas analyzer (System 2001, Medical Graphics, St. Paul,
Minn). This technique, which relies on the determination of oxygen consumption and the partial pressure of carbon dioxide in mixed venous blood (by the rebreathing technique) for calculation of the cardiac output, in our laboratory gives results similar to thermodilution-derived measurements of cardiac output. Forearm blood flow was measured by venous occlusion plethysmography. The arm was elevated slightly above the level of the right atrium, and then forearm blood flow measurements were made with a mercury-filled Silastic strain gauge connected to a plethysmograph, which by calibration allowed blood flow results to be expressed in milliliters per 100 milliliters tissue per minute. A cuff placed on the upper arm was rapidly inflated to occlude venous return while a cuff at the wrist was inflated to 200 mm Hg to exclude the circulation of the hand. The average forearm blood flow was derived from five measurements performed every 20 seconds. The forearm vascular resistance was calculated as the ratio of the mean arterial pressure to forearm blood flow.

Biochemical assays. Blood samples for catecholamine assays were immediately transferred to ice-chilled tubes containing EGTA and reduced glutathione, then centrifuged at 4°C. Plasma samples were then stored at −70°C until assay. Plasma concentrations of endogenous and radiolabeled norepinephrine and DHPG were determined by high-performance liquid chromatography with electrochemical detection as previously described. The integration of a fraction collector allowed the separation of tritiated norepinephrine and its tritiated metabolite for subsequent counting by liquid scintillation spectroscopy. Plasma renin activity was measured by enzymatic generation of angiotensin I followed by radioimmunoassay of the generated angiotensin I. Whole-blood assays of cyclosporine and its metabolites were kindly performed by the Biochemistry Department of the Alfred Hospital by an immunoassay method (TDX, Abbot, Australia).

Statistical analysis. Results are expressed as mean±SEM. The comparison of group means was performed by an unpaired Student’s t test or the Wilcoxon signed rank test (when data were not normally distributed). Serial measurements were analyzed by two-way ANOVA, with post hoc testing performed with the least significant difference method. The null hypothesis was rejected at P<.05.

Results

Hemodynamics

Mean arterial blood pressure in the cardiac transplant patients (recorded before cyclosporine dosing) was significantly higher than in age-matched controls (112±4 vs 87±4 mm Hg; P=.001). In cardiac transplant patients, the cardiac output before cyclosporine dosing was 3.7±0.4 L/min, and the total peripheral resistance was 31.3±6.1 mm Hg·L⁻¹·min⁻¹. The acute administration of cyclosporine had no effect on mean arterial blood pressure (3±2.3 mm Hg, ±SED) over the 2-hour study period (Fig 1A), despite an average increase in whole-blood cyclosporine levels of 133%, from a mean of 605 μg/L to 1411 μg/L (P<.001, Fig 1B). In addition, cyclosporine therapy did not alter cardiac output during this period of observation (Fig 1C).

Renal blood flow was significantly lower in the heart transplant recipients compared with control subjects before acute cyclosporine dosing (680±88 vs 1285±58 mL/min; P<.001). In response to cyclosporine dosing, a progressive decline in renal blood flow was demonstrated, with a reduction of 37% at the 2-hour measurement (P<.001; Fig 2A). In the three transplant patients not receiving cyclosporine, renal blood flow was unchanged over 2 hours of observation (7.0±18.6 mL/min, ±SED). The change in renal blood flow in patients receiving cyclosporine was attributable to a progressive rise in renal vascular resistance, because mean arterial pressure was not altered over this period. In contrast, forearm blood flow progressively rose after the administration of cyclosporine (Fig 2B), increasing from 1.7±0.3 to 3.1±0.5 mL·min⁻¹·100 mL tissue⁻¹ (P<.001), reflecting a 42% reduction in forearm vascular resistance. Total peripheral resistance, however, was unchanged (Fig 2C).

Norepinephrine Kinetics

The concentration of norepinephrine in arterial plasma was similar in the control subjects and heart transplant recipients studied 2 hours after cyclosporine dosing (1104±163 vs 1468±223 pmol/L). The rate of
total norepinephrine spillover into the circulation was also similar in control subjects and transplant patients (2618±313 vs 3070±538 pmol/min). The whole-body clearance rate for norepinephrine was also similar for healthy control subjects and the transplant recipients (2.44±0.10 vs 2.35±0.20 L/min), as was the spillover of norepinephrine from the kidneys into the renal circulation (573±95 pmol/min in healthy subjects vs 579±124 pmol/min in transplant recipients). In response to acute oral administration of cyclosporine, neither the whole-body nor renal norepinephrine spillover rates were observed to change (Fig 3). In the three time-control subjects not receiving cyclosporine acutely, whole-body and renal norepinephrine also remained unchanged after 2 hours of observation.

The arterial plasma renin activity was 0.92±0.3 μg·L⁻¹·h⁻¹ in the transplant recipients, which did not differ significantly from that of the control subjects (0.75±0.3 μg·L⁻¹·h⁻¹). The renal release rate of renin was also not significantly different for control subjects and transplant recipients.

To test for effects of cyclosporine on the reuptake or intraneuronal metabolism of norepinephrine, the fractional extraction of tritiated norepinephrine across the renal circulation and the production of ³H-DHPG were determined. The fractional extraction of norepinephrine was 53±3% in transplant recipients 2 hours after cyclo-

**Fig 3.** Graphs showing total (top) and renal norepinephrine (bottom) spillover rates in response to cyclosporine administration.

Cyclosporine and 56±4% in control subjects (P=NS). Additionally, the fractional extraction was not affected acutely by cyclosporine administration. The arterial concentration of tritiated DHPG was also similar between control subjects and transplant recipients (31.2±3.9 vs 31.2±3.1 dpm/mL). The renal production of ³H-DHPG was also similar in the two groups (control subjects vs transplant patients, 8200±6120 vs 8170±2810 dpm/min).

**Microneurography**

Microneurographic recordings (Fig 4) of sympathetic nerve activity in the peroneal nerve demonstrated an average burst frequency of 30.6±7.6 bursts per minute (37.9±10.1 bursts per 100 beats) immediately before cyclosporine dosing in the transplant recipients. Healthy control subjects had an average burst frequency of 25.8±1.6 bursts per minute (41.3±2.3 bursts per 100 beats), which did not differ significantly from that observed in the transplant recipients. After cyclosporine administration in the transplant patients, sympathetic burst activity (followed for up to 120 minutes) remained unchanged (Fig 5), although only three subjects were studied at the final time point because of instability of the recording site in the other three subjects.

**Discussion**

Our study is in agreement with the widely recognized observation that cardiac transplant recipients treated with cyclosporine have a higher blood pressure than age-matched control subjects. The elevation of blood pressure was associated with a normal or mildly reduced cardiac output and an elevation of total peripheral resistance, similar to the findings reported by Greensberg et al. Furthermore, we found that transplant patients receiving cyclosporine had reduced renal blood flow compared with age-matched control subjects. The
Fig 4. Representative traces showing microneurographic recordings of sympathetic nerve activity (SNA) from the peroneal nerve with associated ECG activity from normal subjects and cyclosporine-treated cardiac transplant patients. SNA is quantified as bursts per minute (b/min) and bursts per 100 heart beats (b/100HB).

Acute elevation in whole-blood cyclosporine levels that follows oral administration was associated with an additional decline in renal blood flow, by 37% at 2 hours after dose, whereas in the three transplant recipients acting as time controls, renal blood flow was unchanged over the 2-hour observation period.

Cyclosporine therapy has generally been shown to reduce both glomerular filtration rate and renal plasma flow,24,25 with a concomitant fall in the fractional excretion of sodium and an expansion of the extracellular fluid volume. The mechanism responsible for this effect of cyclosporine has been the subject of much controversy. A role for enhanced sensitivity to a variety of vasoconstrictors, including norepinephrine, angiotensin II, and arginine vasopressin, has been suggested, in addition to increased production of thromboxane A2 and endothelin.26-28 In humans, cyclosporine has been shown to impair endothelium-mediated vasodilation in subcutaneous resistance arteries,29 although what role these vessels might play in the determination of peripheral vascular resistance in vivo is unclear. In a recent report by Carrier et al.,30 however, the renovascular effects of cyclosporine were not attenuated by $\alpha$-adrenergic blockade or thromboxane receptor antagonism, and the stimulated release of endothelium-derived relaxing factor (by infusion of acetylcholine directly into the renal artery) was preserved. Alternatively, a neural basis for cyclosporine-mediated renal vasoconstriction has been proposed on the basis of observations of increased renal catecholamine concentrations31 and renal sympathetic nerve activity.8 This neural hypothesis, however, fails to explain the observations that renal sympathectomy does not ameliorate the renal vasoconstrictor effect of cyclosporine either in an experimental model30 or during the early phase after renal transplantation32 when the renal allograft is denervated.

Our results using two complementary techniques for assessing the activity of the sympathetic nervous system (norepinephrine kinetics and microneurography) do not support the hypothesis that cyclosporine therapy causes sympathectomy in humans, either during chronic therapy or in response to acute elevations of blood levels of cyclosporine in the postdosing period. Arterial concentrations of norepinephrine and the rate of norepinephrine spillover into plasma in cyclosporine-treated cardiac transplant recipients were similar to those of age-matched controls. Furthermore, the renal vasoconstriction associated with cyclosporine therapy was not associated with elevated renal norepinephrine spillover. Previously, this methodology has shown that renal norepinephrine spillover measurements faithfully reflect renal sympathetic nerve firing in animals over a range of renal blood flows.33 In humans, total norepinephrine spillover measurements are sufficiently sensitive to detect pharmacological suppression of sympathetic nerve neurotransmitter release by clonidine and the ganglionic blocking drug arfonad.34 Similarly, reduction in total norepinephrine spillover is seen with the sympathetic withdrawal accompanying fainting reactions and physical conditioning through exercise training and with the sympathetic nerve failure of idiopathic
peripheral autonomic insufficiency.34 In contrast, sympathetic nervous activation accompanying cardiac failure, upright posture, cirrhosis, and mental and physical stress is associated with readily detectable increments in total norepinephrine spillover.34 Measurements of human renal norepinephrine spillover are similarly sensitive to changes in renal sympathetic nerve firing. Detectable reductions in renal norepinephrine spillover are associated with clonidine treatment and exercise training, whereas increased spillover rates are associated with sodium restriction, heart failure, and cirrhosis.34 Thus, it is unlikely that in cyclosporine-treated patients our calculated renal spillover rates of norepinephrine were spuriously low in the face of low renal blood flow.

In testing for possible separate effects of cyclosporine on the sympathetic neuroeffector junction (including the neuronal reuptake of norepinephrine), we found that the fractional extraction of tracer norepinephrine across the kidneys was not altered by cyclosporine. This finding reinforces our conclusion that a reduction in renal blood flow to the extent observed is unlikely to have confounded our measurements of renal norepinephrine spillover by a mechanism such as a reduction in flow-dependent washout.35 In addition, the arterial concentration of \textsuperscript{3}H-DHPG formed by intraneuronal metabolism of norepinephrine after neuronal uptake was normal. This implies that the disposition of neurally released norepinephrine is not affected by cyclosporine.

The finding of reduced renal blood flow in the cardiac transplant recipient group before cyclosporine dosing (and presumably at trough blood levels) could be explained by a number of mechanisms. First, the trough levels (605 µg/L) may still produce a renal vasoconstrictor effect alone. In addition, a chronic nephrotoxic effect of cyclosporine and the potential effect of severe heart failure (before transplantation) on renal function may play an additional role.

Cyclosporine-induced hypertension in humans has been characteristically associated with normal or low renin levels.5,36 This contrasts with the finding in young essential hypertensive subjects (without transplants) who are commonly noted to have high plasma renin activity and renal renin release rates.37 This group of hypertensive patients has shown increased sympathetic activity measured by either whole-body and renal nor- epinephrine spillover or microneurography.38 Increased plasma renin activity in this group is explained in part by the fact that renin release from the kidneys is under sympathetic control.39 In keeping with our finding that whole-body and renal spillover rates of norepinephrine in our transplant patient group were similar to those of the control group, we also noted that plasma renin activity (and renal release) did not differ significantly from healthy control subjects. If cyclosporine were to cause hypertension via sympathoexcitation, elevation of plasma renin activity would be expected.

Recently, Scherrer et al\textsuperscript{4} used microneurographic techniques to record sympathetic nerve activity in the peroneal nerve in cardiac transplant recipients, some of whom were not receiving cyclosporine as a part of their immunosuppressive regimen. In their study, patients treated with cyclosporine had higher rates of sympathetic nerve firing, suggesting that cyclosporine-induced hypertension is neurogenic, caused by sympathetic acti-
Direct recording of muscle sympathetic nerve activity in the upper limb was not performed, however, and since significant differences in nerve activity may exist in the upper and lower limb, it is not possible to draw firm conclusions about the mechanism of the forearm vasodilation observed in this study.

In conclusion, we observed that renal, skeletal muscle, and total sympathetic nervous system activity was normal in relation to peak and trough levels of cyclosporine, according to dosing regimens used in routine clinical practice. The use of the immunosuppressive agent was associated with nonneural renal vasoconstriction, which appeared to follow a time course related to rising blood levels of the drug. The hypertension associated with cyclosporine therapy is a chronic manifestation of its use, since acute fluctuations in cyclosporine levels were not associated with blood pressure changes after dosing. The practical implication of the findings arising from this study is that cyclosporine-induced hypertension does not appear to be adrenergically driven, at least in its chronic clinical form, and is characterized by renal vasoconstriction. Therefore, it may be appropriate to treat this form of hypertension with nonnitradienergic antihypertensive medications. Furthermore, comparative studies of calcium antagonists (notably nifedipine) and prazosin have shown that the former has protective actions against the nephrotoxic effects of cyclosporine in addition to effective antihypertensive action. Despite the adverse hypertensive and nephrotoxic actions, cyclosporine remains at present a valuable immunosuppressive agent, with valuable effects on allograft and patient survival after transplantation.

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