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CYCLOSPORINE-INDUCED SYMPATHETIC ACTIVATION AND HYPERTENSION AFTER HEART TRANSPLANTATION

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Abstract *Background.* Hypertension is a frequent complication of cyclosporine-induced immunosuppression, but the underlying mechanism is unknown. In anesthetized animals, the administration of cyclosporine increases sympathetic-nerve discharge, which may contribute to hypertension.

Methods. To determine whether cyclosporine-induced hypertension is accompanied by sustained sympathetic neural activation in patients, we recorded sympathetic action potentials using intraneural microelectrodes (in the peroneal nerve) in heart-transplant recipients receiving azathioprine and prednisone alone (n = 5) or in combination with cyclosporine (n = 14). We performed the same studies in eight patients with myasthenia gravis who were receiving cyclosporine and eight who were not, in five patients with essential hypertension, and in nine normal controls.

Results. Heart-transplant recipients receiving cyclosporine had higher mean arterial blood pressure (±SE) than those not receiving cyclosporine (112±3 vs. 96±4 mm Hg; $P<0.05$) and a 2.7-fold higher rate of sympathetic-nerve firing (80±3 vs. 30±4 bursts per minute; $P<0.05$). For patients with myasthenia gravis, similar doses of cyclosporine were associated with smaller elevations in mean arterial blood pressure (100±2 mm Hg, as compared with 91±4 mm Hg in those not receiving cyclosporine; $P<0.05$) and in the rate of sympathetic-nerve firing (46±3 bursts per minute, as compared with 25±4 bursts per minute; $P<0.05$). Sympathetic activity in patients with heart transplants or myasthenia gravis who were not being treated with cyclosporine was no different from that in patients with essential hypertension or in normal controls.

Conclusions. Cyclosporine-induced hypertension is associated with sympathetic neural activation, which may be accentuated by the cardiac denervation that results from heart transplantation. (N Engl J Med 1990; 323: 693-9.)

CYCLOSPORINE is a novel immunosuppressive agent that has greatly enhanced long-term survival after organ transplantation[1] and has proved beneficial in the treatment of many autoimmune diseases.[2-5] However, cyclosporine has also produced a new form of hypertension.[1,6,7] The hypertensive effect of cyclosporine has been demonstrated most vividly in heart-transplant recipients, in whom the incidence of hypertension has increased from less than 20 percent in the precyclosporine era to more than 90 percent currently.[1,8-10] This hypertension typically is moderate to severe and often requires treatment with a number of antihypertensive agents. Thus, hypertension has become one of the most important problems in the medical care of heart-transplant recipients. Although this form of hypertension has been attributed directly to the administration of cyclosporine, the underlying mechanism is unknown.

In anesthetized animals, the short-term administration of cyclosporine stimulates sympathetic-nerve discharge.[11,12] In heart-transplant recipients, this sympathoexcitatory effect of cyclosporine may be accentuated because cardiac transplantation interrupts the afferent (as well as efferent) neural connections from the transplanted ventricles to the central nervous system and thus removes ventricular-baroreceptor restraint on sympathetic outflow.[13,14]

Accordingly, the aims of this study were to deter-

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mine whether the long-term administration of cyclosporine causes sustained sympathetic neural activation in humans and whether this effect is evident mainly in heart-transplant recipients, who have ventricular-baroreceptor denervation. To accomplish these aims, we performed microelectrode recordings of postganglionic sympathetic action potentials in heart-transplant recipients (denervated hearts) and in patients with myasthenia gravis (innervated hearts) undergoing immunosuppressive treatment with azathioprine and prednisone alone or in combination with cyclosporine.

Methods

Selection of Subjects

Four groups of subjects were studied: heart-transplant recipients, patients with myasthenia gravis, patients with essential hypertension, and control subjects. We studied 14 heart-transplant recipients who were being treated with azathioprine and prednisone plus cyclosporine (transplantations performed at either the University of Wisconsin at Madison or the University of Texas Southwestern Medical Center at Dallas) and 5 heart-transplant recipients who were being treated with azathioprine and prednisone alone and had never received cyclosporine (transplantations performed at either the Medical College of Virginia or the McGuire Veterans Affairs Medical Center in Richmond). We studied 14 patients with myasthenia gravis who were enrolled in a randomized, double-blind, crossover trial of cyclosporine and placebo. During the study period, one patient was switched from cyclosporine to placebo, and another patient from placebo to cyclosporine. We also studied five patients with uncomplicated essential hypertension and nine healthy, normotensive, middle-aged control subjects. The mean (±SE) ages of the four groups of subjects were similar: 47±4, 46±6, 49±2, and 45±3 years. The protocol was approved by the institutional review board on human investigation at all the facilities, and all subjects provided written informed consent before participation.

At the time of the study, none of the transplant recipients had any evidence of transplant rejection or congestive heart failure, as assessed by history and physical examination (all were in New York Heart Association class I), electrocardiography, multigated acquisition scanning at rest and during exercise, echocardiography, and cardiac catheterization with endomyocardial biopsy. None of the patients had orthostatic hypotension. All the patients had serum creatinine levels of less than 160 μmol per liter.

In all transplant recipients, both the recipient and donor hearts were in normal sinus rhythm. The cyclosporine-treated heart-transplant recipients and those not treated with cyclosporine were taking similar doses of azathioprine (mean ±SE, 110±15 vs. 130±10 mg per day; $P>0.1$) and prednisone (15±2 vs. 13±3 mg per day; $P>0.1$). One cyclosporine-treated patient with myasthenia gravis and two who had not received cyclosporine were taking azathioprine (100 mg per day). The average dose of prednisone tended to be higher in the patients with myasthenia gravis who had not received cyclosporine than in those who had (27.5±5.6 vs. 12.5±10.3 mg per day; $P>0.1$). Transplant recipients and patients with myasthenia gravis were taking similar doses of cyclosporine (3.8±0.3 vs. 3.2±0.8 mg per kilogram of body weight per day; $P>0.1$).

Essential hypertension was present in two heart-transplant recipients before transplantation and in two patients with myasthenia gravis before the administration of cyclosporine. All antihypertensive medications were withheld for 72 to 96 hours before the study, except in the case of two heart-transplant recipients in whom it was deemed unsafe to do so.

General Procedures

All experiments were performed after a meal while the subjects were supine. Rates of both the donor heart and the recipient's atrial remnant (electrocardiography), respiratory excursions (pneumography), and efferent muscle sympathetic-nerve activity were recorded continuously on a TEAC R 71 tape recorder (Tokyo, Japan) and later transcribed to hard copy with a Gould ES1000 electrostatic recorder (Oxnard, Calif.). Respiratory excursions were monitored to detect inadvertent performance of a Valsalva maneuver or prolonged expiration, because these respiratory maneuvers markedly stimulate muscle sympathetic outflow.[15] Blood pressure was measured in the right arm with an automated sphygmomanometer (Dinamap, Critikon, Tampa, Fla.).

Recording of Sympathetic-Nerve Discharge

Multiunit recordings of postganglionic sympathetic-nerve activity were obtained with unipolar tungsten microelectrodes inserted selectively into muscle nerve fascicles of the peroneal nerve posterior to the fibular head according to the technique of Vallbo et al.[16] Briefly, the neural signals were amplified 20,000 to 50,000 times, filtered (bandwidth, 700 to 2000 Hz), rectified, and integrated (time constant, 0.1 second) to obtain a mean-voltage display of sympathetic activity. A recording of sympathetic activity was considered acceptable when the neurograms revealed spontaneous, pulse-synchronous bursts of neural activity, with the largest bursts showing a minimal signal-to-noise ratio of 3:1. In each experiment, we documented that we were recording sympathetic outflow to skeletal muscle by demonstrating that the neural activity had no response to arousal stimuli (loud noise or skin pinch) but had a characteristic biphasic response to the Valsalva maneuver.[15] This response consists of sympathetic activation during Phases II and III (decrease in blood pressure) followed by sympathetic inhibition during Phase IV (increase in blood pressure on release), the latter being used to define the noise level.

Sympathetic bursts were detected by inspection of the filtered and mean-voltage neurograms. A deflection on the mean-voltage display was counted as a burst if it had a minimal signal-to-noise ratio of 2:1 and was pulse-synchronous (with an interburst interval equal to or a multiple of the RR interval). The interobserver and intraobserver variabilities in identifying bursts are less than 10 percent and less than 5 percent, respectively.[17] Inadvertent contraction of the leg muscles adjacent to the recording electrode produces electromyographic artifacts that are easily distinguished from sympathetic bursts; neurograms that revealed such artifacts were excluded from analysis. Nerve traffic was expressed as the number of bursts of sympathetic activity per minute and as the number of sympathetic bursts per 100 heartbeats, the latter providing a measure of sympathetic activity that is controlled for heart rate. These indexes of sympathetic-burst frequency have been shown to be remarkably stable when a given subject is studied on repeated occasions; the intrasubject variability is less than 15 percent.[16] No attempt was made to measure sympathetic-burst amplitude, which is dependent on the position of the recording electrode in the nerve fascicle.

In all experiments, nerve recordings were analyzed with the investigator blinded to the group assignment of the patients. In the studies performed in patients with myasthenia gravis, all data were collected and analyzed in a double-blind fashion.

Measurement of Calf Blood Flow

While recording sympathetic outflow to calf muscles in one leg, we simultaneously measured calf blood flow in the contralateral leg. Calf blood flow was measured by venous-occlusion plethysmography.[18] The calf was elevated above the level of the right atrium to collapse the veins. The circulation to the foot was arrested during blood-flow determinations, which were performed at 15-second intervals. Calf vascular resistance was calculated as the mean arterial pressure (one third of the pulse pressure plus diastolic pressure) in millimeters of mercury divided by calf blood flow in milliliters per minute per 100 ml of tissue.

Determination of Plasma Norepinephrine Concentration

In 10 heart-transplant recipients taking cyclosporine, 5 transplant recipients not taking cyclosporine, and 9 normotensive control subjects, we obtained venous blood samples from an indwelling

cannula in a forearm vein for the determination of norepinephrine levels; 10-ml aliquots were withdrawn after the subject had rested quietly for 30 minutes. The samples were collected in prechilled tubes treated with heparin and promptly centrifuged at 4°C. Norepinephrine levels were assayed by high-performance liquid chromatography with an electrochemical detector (SmithKline BioScience Laboratories, Van Nuys, Calif.). The assay was sensitive to 10 pg of norepinephrine per milliliter, with a coefficient of variation of 10 percent.

Experimental Protocol

To ensure a stable level of base-line values, all subjects rested quietly for 30 minutes, after which nerve activity and blood flow at rest were recorded for four 15-minute periods. The values for sympathetic activity and calf blood flow represent the mean of these four measurement periods. In 7 of the 14 heart-transplant recipients who received cyclosporine, neural recordings were performed on two consecutive days.

To document vagal denervation of the transplanted heart, we measured donor and recipient heart-rate responses to static handgrip. One minute of static handgrip at one third of the maximal voluntary contraction had no effect on the ventricular rate in any of the heart-transplant recipients, even though this maneuver increased the atrial remnant rate by 8±1 beats per minute ($P<0.05$).

Statistical Analysis

The mean differences across groups were compared by analysis of variance with least-significant-difference post hoc tests. Student's two-tailed t-test was used for paired comparisons within groups. Correlation coefficients were calculated according to the method of least squares. A P value of less than 0.05 was considered to indicate significance. Results are expressed as means ±SE.

Results

The characteristics of the heart-transplant recipients and the patients with myasthenia gravis, including individual values of sympathetic-nerve activity, are shown in Tables 1 and 2. Values of mean arterial pressure, sympathetic activity, calf blood flow, and vascular resistance for all four groups of subjects are shown in Table 3.

In heart-transplant recipients treated with cyclosporine, the rate of muscle sympathetic discharge was 2.9 times that in normal controls: 80±3 as compared with 28±4 sympathetic bursts per minute ($P<0.05$) (Table 3 and Fig. 1). Similarly, the discharge rate in the cyclosporine-treated recipients was 2.7 times that in the recipients not treated with cyclosporine ($P<0.05$). In contrast, sympathetic activity was indistinguishable from normal both in heart-transplant recipients who were not treated with cyclosporine and in patients with essential hypertension (Table 3 and Fig. 1). Although ventricular rates were similar in both groups of heart-transplant recipients (91±4 vs. 90±4 beats per minute), sympathetic nerves fired during 88±2 percent of cardiac cycles in the group receiving cyclosporine but only during 34±6 percent of cardiac

Table 1. Characteristics of the Heart-Transplant Recipients.

Patient No.	Age/Sex	Time since Transplantation	Heart Rate		Blood Pressure	Sympathetic-Nerve Activity	Resting LVEF*	Cyclosporine	Serum Creatinine	Antihypertensive Medications
			Atrial Remnant	Transplant Ventricle						
		mo	*beats/min*		*mm Hg*	*bursts/min*	*%*	*mg/kg/day*	*μmol/liter*	
Receiving cyclosporine										
1	59/M	4	67	86	137/88	81	49	5.2	113	Bumetanide
2	50/M	18	63	96	143/101	66	55	4.4	115	Furosemide
3	45/M	2	90	68	170/105	62	62	3.4	133	—
4	47/F	18	86	104	128/88	87	57	3.3	106	Bumetanide
5	41/M	11	66	61	135/85	60	83	4.6	141	Enalapril Bumetanide
6	42/M	16	94	104	130/89	94	58	5.2	124	Bumetanide
7	32/M	5	71	100	136/85	86	46	3.5	133	Enalapril Furosemide
8	49/M	9	85	90	170/102	72	60	3.5	159	Nifedipine
9	54/M	12	86	88	155/100	74	60	3.0	159	Enalapril
10	54/M	22	76	104	152/95	92	49	1.8	106	Clonidine Enalapril
11	59/M	11	78	108	153/101	96	43	3.6	88	Clonidine Verapamil Bumetanide
12	55/M	13	62	88	140/101	73	51	3.6	159	Clonidine Enalapril Furosemide Verapamil
13	55/M	46	—	89	160/111	88	50	3.3	133	Clonidine† Enalapril Furosemide
14	26/M	10	80	96	157/98	83	66	4.6	124	Clonidine†
Not receiving cyclosporine										
15	37/M	76	73	94	120/75	34	50	—	80	—
16	50/M	74	81	110	136/90	25	50	—	106	Diltiazem
17	54/M	82	82	82	132/80	34	55	—	97	—
18	54/M	75	85	100	140/86	18	53	—	80	—
19	34/M	80	55	81	110/70	41	60	—	80	—

*LVEF denotes left ventricular ejection fraction.

†Antihypertensive medication was not discontinued before the study.

Table 2. Characteristics of the Patients with Myasthenia Gravis.

Patient No.	Age/Sex	Duration of Cyclosporine Therapy	Heart Rate	Blood Pressure	Sympathetic-Nerve Activity	Cyclosporine	Serum Creatinine	Antihypertensive Medications
		mo	*beats/min*	*mm Hg*	*bursts/min*	*mg/kg/day*	*μmol/liter*	
Receiving cyclosporine								
1*	36/M	17	72	132/80	49	1.0	106	Verapamil
2*	75/M	2	50	160/86	47	5.0	115	—
3	41/M	12	82	130/90	46	1.8	97	Verapamil Captopril
4	58/M	12	76	145/86	50	1.2	133	Hydrochlorothiazide Verapamil Enalapril
5	37/M	2	58	124/78	35	5.9	124	—
6	42/F	9	64	136/79	34	5.7	80	—
7	67/M	36	52	136/84	52	1.2	80	Atenolol
8	73/M	24	70	134/74	58	3.4	97	Hydrochlorothiazide
Not receiving cyclosporine								
1*	36/M	—	72	132/80	49	1.0	106	Verapamil
2*	75/M	—	50	160/86	47	5.0	115	—
9	33/M	—	68	121/77	32	—	115	Verapamil
10	31/M	—	56	114/67	15	—	97	—
11	29/M	—	65	120/69	17	—	133	—
12	20/M	—	80	137/77	37	—	80	—
13	54/F	—	70	134/81	9	—	80	—
14	32/F	—	74	104/56	30	—	71	—

*The patient received both cyclosporine and placebo.

cycles in the group not treated with cyclosporine ($P<0.05$) (Table 3).

In the transplant recipients treated with cyclosporine, sympathetic discharge was not significantly correlated with the time that had elapsed since transplantation ($r = 0.34$, $P>0.1$). In the three heart-transplant recipients receiving cyclosporine who had stopped taking clonidine before the study, the rate of sympathetic discharge (87±7 bursts per minute) was similar to that in the nine transplant recipients who had never received clonidine (76±4 bursts per minute) and in the two patients in whom clonidine therapy was continued (88 and 83 bursts per minute).

In the patients with myasthenia gravis, sympathetic discharge was 1.8 times higher in the cyclosporine group than in the placebo group: 46±3 as compared with 25±4 bursts per minute ($P<0.05$) (Table 3). Sympathetic activity increased from 32 to 47 bursts per minute in the one patient with myasthenia gravis who was switched from placebo to cyclosporine, and decreased from 49 to 26 bursts per minute in the patient who was switched from cyclosporine to placebo (Fig. 2).

Cyclosporine treatment was associated with higher blood pressure and calf vascular resistance in heart-transplant recipients and in patients with myasthenia gravis than in their respective non-cyclosporine-treated controls (Table 3). However, both mean arterial pressure (112±3 vs. 100±2 mm Hg) and sympathetic activity (80±3 vs. 46±3 bursts per minute) were significantly higher ($P<0.05$) in heart-transplant recipients than in patients with myasthenia gravis taking similar doses of cyclosporine.

Figure 3 shows the relation between sympathetic-nerve activity and plasma norepinephrine levels in heart-transplant recipients and healthy control sub-

Table 3. Characteristics of the Four Study Groups.

Variable	Heart-Transplant Recipients		Patients with Myasthenia Gravis		Patients with Essential Hypertension (N = 5)	Normotensive Control Subjects (N = 9)
	Cyclosporine (N = 14)	No Cyclosporine (N = 5)	Cyclosporine (N = 8)	No Cyclosporine (N = 8)		
Mean arterial pressure (mm Hg)	112±3*†‡	96±4*	100±2*†	91±4	108±3*	85±2
Sympathetic-nerve activity						
Bursts/min	80±3*†‡	30±4	46±3*†	25±4	29±7	28±4
Bursts/100 heartbeats	88±2*†‡	34±6	72±6*†	39±5	42±10	44±5
Calf blood flow (ml/min/100 ml)	2.0±0.3*†	2.8±0.2	2.1±0.2*	2.5±0.2	2.5±0.1	3.0±0.3
Calf vascular resistance (units)	55.4±5.5*†	34.2±4.3	46.4±4.2*†	36.2±2.6	40.2±1.8	30.7±3.2

*$P<0.05$ for the comparison with normotensive control subjects.

†$P<0.05$ for the comparison with patients not treated with cyclosporine.

‡$P<0.05$ for the comparison with cyclosporine-treated patients with myasthenia gravis.

jects. Although there was considerable overlap between groups, plasma norepinephrine levels were higher in the transplant recipients who received cyclosporine than in those who did not or in normal control subjects: 1.55±0.15, 1.03±2.7, and 0.90±0.11 nmol per liter (262±26, 174±45, and 152±18 pg per milliliter), respectively ($P<0.05$). Plasma norepinephrine concentrations showed a significant correlation with sympathetic activity in the heart-transplant recipients who received cyclosporine ($r = 0.81$, $P<0.01$); in contrast, no such relation was observed in the transplant recipients who did not receive cyclosporine or in the normal control subjects.

Discussion

We used intraneural microelectrodes to measure sympathetic discharge in two groups of patients undergoing immunosuppressive treatment with or without cyclosporine. The principal conclusion of our study is that cyclosporine treatment is accompanied by sustained sympathetic activation both in heart-transplant recipients and in patients with myasthenia gravis. This sympathetic activation is directly related to the administration of cyclosporine and appears to be accentuated by the cardiac denervation that results from heart transplantation.

Previous studies in heart-transplant recipients suggested that cyclosporine did not cause sympathetic overactivity because plasma and urinary catecholamine concentrations were normal.[8,19] In our heart-transplant recipients receiving cyclosporine, plasma norepinephrine levels also were within the normal range of the assay but nevertheless were 50 percent higher than in transplant recipients not receiving cyclosporine. This subtle elevation in plasma norepinephrine was accompanied by marked increases in sympathetic discharge and regional vascular resistance, indicating that sympathetic activation cannot be excluded on the basis of "normal" norepinephrine levels.

Increased sympathetic activity in patients receiving cyclosporine was not related to the withdrawal of clonidine or to preexisting essential hypertension. None of the patients with myasthenia gravis were taking clonidine before the study. In the three heart-transplant recipients in whom clonidine was withdrawn before the study, the level of sympathetic activation was similar to but not more than that seen in the nine transplant recipients who had never received clonidine. Sympathetic activity was normal in patients with uncomplicated essential hypertension, which confirms previous reports[20,21] and indicates that sympathetic activation during cyclosporine treatment is not a nonspecific autonomic response to chronic hypertension.

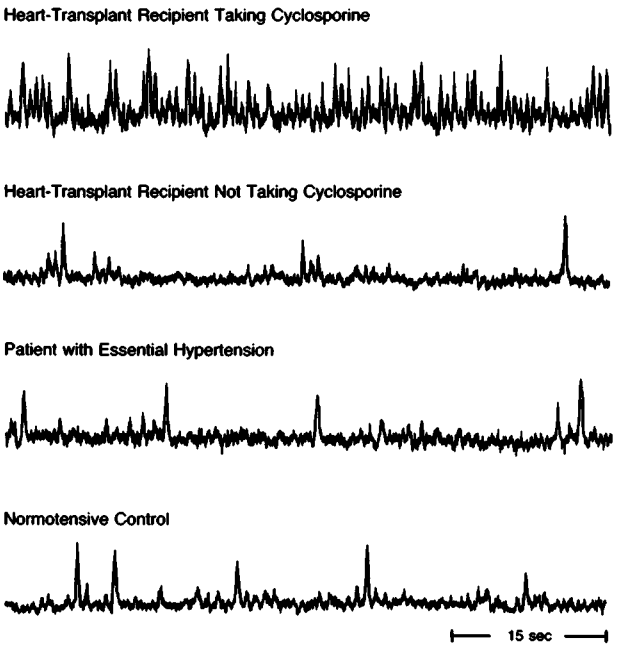

Figure 1. Recordings of Muscle Sympathetic-Nerve Activity in a Heart-Transplant Recipient Taking Cyclosporine, a Heart-Transplant Recipient Not Taking Cyclosporine, a Patient with Essential Hypertension, and a Normotensive Control Subject.

On these mean-voltage displays of muscle sympathetic-nerve activity, each peak represents a spontaneous burst of sympathetic discharge. The frequency of sympathetic neural firing was much higher than normal in the heart-transplant recipient treated with cyclosporine. In contrast, sympathetic activity was normal both in the heart-transplant recipient who was not taking cyclosporine and in the patient with essential hypertension.

Among the heart-transplant recipients who received cyclosporine, the degree of sympathetic overactivity was unrelated to the time that had elapsed since transplantation. This finding suggests that the lower levels of sympathetic activity in the heart-transplant recipients who had never received cyclosporine were not caused by either the gradual resolution of lingering sympathetic activation from preexisting heart failure[22-24] or the gradual reinnervation of the transplanted heart. Reflex neurohumoral abnormalities accompanying heart failure resolve within the first few weeks or months after successful cardiac transplantation.[19,25] Most human cardiac allografts do not undergo func-

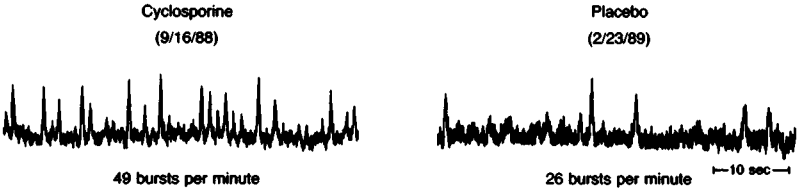

Figure 2. Recordings of Muscle Sympathetic-Nerve Activity in One Patient with Myasthenia Gravis Obtained during Treatment with Cyclosporine and Three Months after Cyclosporine Had Been Replaced by Placebo.

In this patient, the rate of sympathetic firing decreased when cyclosporine was discontinued.

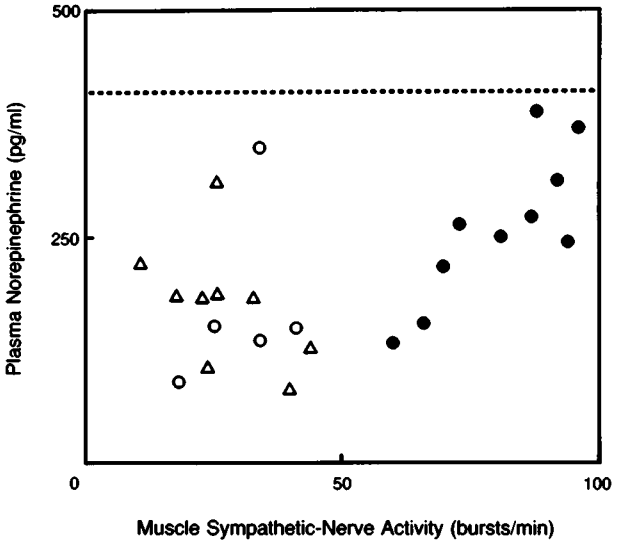

Figure 3. Relation between Muscle Sympathetic-Nerve Activity and Plasma Norepinephrine Levels in 10 Heart-Transplant Recipients Taking Cyclosporine (Solid Circles), 5 Heart-Transplant Recipients Not Taking Cyclosporine (Open Circles), and 9 Normal Control Subjects (Triangles).

In all the heart-transplant recipients, plasma norepinephrine levels fell within the normal range of the assay (below the dashed line). Although there was considerable overlap between norepinephrine levels in the different groups of subjects, these levels on average were higher in heart-transplant recipients receiving cyclosporine than in either patients who had never received cyclosporine or normal control subjects. In contrast, there was no overlap between the increased levels of sympathetic firing in the cyclosporine-treated transplant recipients and the normal levels of sympathetic firing in the other two groups. To convert values for plasma norepinephrine to nanomoles per liter, multiply by 0.005911.

tional extrinsic reinnervation[14,26-32]; indeed, in our heart-transplant recipients, ventricular heart rates were dissociated from the rates of innervated atrial remnants at rest and failed to increase during static handgrip — a maneuver that consistently increased atrial-remnant rates by 8 to 10 beats per minute.

The finding that cyclosporine treatment was associated with increased sympathetic activity in patients with myasthenia gravis as well as in heart-transplant recipients indicates that this effect of cyclosporine does not depend on cardiac (ventricular-baroreceptor) denervation. Such denervation, however, may facilitate the sympathoexcitatory effect of cyclosporine. Similar doses of cyclosporine were associated with larger increases in sympathetic activity and blood pressure in heart-transplant recipients than in patients with myasthenia gravis. Although many mechanisms have been implicated in the pathogenesis of cyclosporine-induced hypertension,[9,33-38] augmented sympathetic activation provides one possible explanation for the greater hypertensive effect of cyclosporine in heart-transplant recipients than in other groups of patients.[1,39]

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CEREBROVASCULAR COMPLICATIONS OF THE USE OF THE "CRACK" FORM OF ALKALOIDAL COCAINE

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Abstract *Background and Methods.* The use of cocaine, especially one of its alkaloidal forms ("crack"), has been increasingly associated with cerebrovascular disease. To clarify the clinical, radiologic, and pathological features of the events associated with cocaine use, we identified 28 patients at four medical centers who had stroke temporally related to the use of alkaloidal cocaine (during or within 72 hours of use).

Results. The 28 patients had the following types of cerebrovascular event: cerebral infarction (n = 18 [2 hemorrhagic; 1 fatal]) in the areas supplied by the middle cerebral artery (n = 10), anterior cerebral artery (n = 3), posterior cerebral artery (n = 1), and vertebrobasilar arteries (n = 4); subarachnoid hemorrhage (n = 5); intraparenchymal hemorrhage (n = 4); and primary intraventricular hemorrhage (n = 1). Eighteen patients (64 percent) had acute neurologic symptoms immediately or within one hour of using cocaine. Fifteen patients (45 percent) with either occlusive or hemorrhagic strokes had severe headache as an early symptom. Vasculitis was not suggested by radiography in any patient, nor was it identified on pathological examination in one patient who died. All the patients were young (mean age, 34 years; range, 23 to 49) and had no other apparent, direct cause of stroke. Other risk factors for stroke among the patients included mild mitral-valve prolapse (n = 4), hypertension (n = 4), cigarette smoking (n = 8), and regular alcohol use (n = 6).

Conclusions. There is a strong temporal association of the use of alkaloidal cocaine with both ischemic and hemorrhagic cerebrovascular events. Cocaine-related stroke probably has many causes. A thorough history focusing on the use of cocaine and toxicologic screening of urine and serum should be part of the evaluation of any young patient with a stroke. (N Engl J Med 1990; 323:699-704.)

NUMEROUS studies have demonstrated an association between cerebrovascular disease and the use of cocaine.[1-34] The appearance in 1983 of commercially prepared alkaloidal cocaine ("crack") escalated an already existing cocaine epidemic.[1,10,35-37] Reports of medical complications of cocaine use, including stroke, have increased as well, although it is unclear whether recent reports of stroke among crack users reflect the spreading epidemic, greater cerebrovascular specificity, higher potency, or a combination of these factors. "Freebasing" (preparing the extract of the almost pure alkaloidal, or freebase, form of the drug) removes cocaine adulterants.[38] By contrast, crack is made simply by heating an aqueous solution of cocaine hydrochloride with sodium bicarbonate or ammonia; the resulting precipitate, unlike freebase cocaine, contains adulterants but is also smokable.

Despite the current widespread use of cocaine, little is known about the detailed clinical, radiologic, and pathological features of the cerebrovascular syndromes associated with use of the alkaloidal form of cocaine. We therefore studied 28 patients with a variety of cerebrovascular complications of the use of crack.

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METHODS

Patients known to have cerebrovascular complications temporally related to the use of alkaloidal cocaine (i.e., occurring during or