Post-carotid endarterectomy hypertension: Association with elevated cranial norepinephrine

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The cause and mechanism of post-carotid endarterectomy hypertension remains unknown. To determine the influence of the sympathetic and renin-angiotensin system, we measured cranial and peripheral plasma levels of catecholamine and renin in patients undergoing carotid endarterectomy. Baseline samples were drawn just before carotid clamping (sample I) and compared with study samples drawn immediately after clamp release (sample II), 2 to 6 hours after surgery (sample III), and then 18 to 24 hours after surgery (sample IV). The patients with post-carotid endarterectomy hypertension had an associated increase of cranial and peripheral norepinephrine levels in the postoperative hypertensive period whereas the patients without post-carotid endarterectomy hypertension did not. This association was most pronounced and statistically significant in cranial samples II ($p = 0.032$) and III ($p = 0.005$). Epinephrine and dopamine values did not correlate with post-carotid endarterectomy hypertension. Renin values were higher in cranial than in peripheral samples at time period 2 ($p = 0.011$), sugestive of a central nervous system Goldblatt phenomenon. However, the renin values did not correlate with post-carotid endarterectomy hypertension. We conclude that post-carotid endarterectomy hypertension is associated with elevated cranial norepinephrine levels, suggestive of a central nervous system sympathomimetic mechanism. Optimal prevention and treatment of this brief but frequently occurring hypertension should include a central-acting sympatholytic agent. (J VASC SURG 1989;9:351-60.)

Approximately 90,000 patients undergo carotid endarterectomy each year, making this procedure the most common peripheral vascular operation performed in the United States today.[1] Postoperative hypertension lasting 12 to 24 hours complicates 19% to 66% of these cases and is associated with a 10% to 47% incidence of postoperative neurologic deterioration.[2-12] In contrast, less than 6% of normotensive or hypotensive patients develop neurologic complications. These statistics translate to approximately 5000 strokes annually associated with carotid endarterectomy and postoperative hypertension. Furthermore, severe intermittent hypertension can augment postischemic brain damage.[13]

The cause and mechanism of this brief but frequently occurring entity, post-carotid endarterectomy hypertension, remains unclear. Towne and Bernhard,[6] Skudlorick and Mooring,[7] and Assiddao et al.[2] noted a correlation of preoperative and postoperative hypertension. Bove et al.[3] and Angell-James and Lumley[14] postulated that surgical manipulation of the carotid bulb caused altered baroreceptor function and thereby induced hypertension through humoral or neural mechanisms. Bunag et al.[15] and Hodge et al.,[16] respectively, finding that acute bilateral carotid occlusion in the dog induces elevated renin and angiotensin levels, concluded that acute cerebral ischemia caused the sympathetic nervous system to stimulate renal renin release, leading to elevated angiotensin levels and thus hypertension. However, Moore and Hall[17] demonstrated that total epidural anesthesia, but not nephrectomy, blocks this hypertensive response, suggesting a sympathetic nervous system mediation unrelated to the kidneys. These studies implicate either a nonrenal source of renin and angiotensin or a sympathetic nervous system neuroamine such as epinephrine and norepinephrine.[18-20] Recently, Smith[21] reported increased

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Table I. Perioperative factors potentially influencing the development of postoperative hypertension (n = 47 cases)

Factor	No.	%
Preoperative hypertension	24	51
Diabetes mellitus	9	19
Carotid stenosis ≥ 75%	36	77
Abnormal neurologic examination	19	40
Anesthetic		
Isoflurane	24	51
Balanced nitrous narcotic	23	49
Carotid shunt	27	57
New postoperative neurologic deficit (all transient)	6	13

intracranial renin levels in patients with post-carotid endarterectomy hypertension and postulated a possible central nervous system Goldblatt phenomenon.

To test these renin and catecholamine hypotheses, we proposed to collect intracranial and peripheral blood samples in patients undergoing carotid endarterectomy, analyze these samples for renin and catecholamine activity, and correlate these activities with post-carotid endarterectomy hypertension. The objectives of this study were to determine whether post-carotid endarterectomy hypertension is associated with elevated plasma renin levels, catecholamine values, or both and whether these humoral factors originate from intracranial or peripheral sources.

MATERIAL AND METHODS

Patient population. Forty-four patients undergoing 47 unilateral or staged bilateral carotid endarterectomies at the University of California, Los Angeles (UCLA) Center for the Health Sciences consented to participate in this study and had blood samples available for analysis. Patients who underwent simultaneous bilateral carotid endarterectomy or other concomitant major operations were excluded. All patients underwent general anesthesia. Patients who were not considered safe or appropriate candidates for general anesthesia were excluded. This study was approved by the UCLA School of Medicine Human Subject Protection Committee.

Definition of hypertension. At least three separate supine cuff and Doppler blood pressure measurements of each arm were obtained before surgery. The higher blood pressure (cuff vs Doppler; right vs left arm) was considered the patient's true blood pressure. Preoperative hypertension was defined as systolic blood pressure ≥140 mm Hg or pressure diastolic ≥90 mm Hg on three different determinations before surgery. A patient with a history of hypertension and currently taking antihypertensive medica-

tions was considered to have preoperative hypertension regardless of the preoperative blood pressure measurements. Before surgery in all patients blood pressure was medically controlled to systolic readings >160 mm Hg and diastolic readings <100 mm Hg. All preoperative antihypertensive medications were continued during surgery to prevent rebound hypertension, which is not to be confused with post-carotid endarterectomy hypertension.

Post-carotid endarterectomy hypertension was defined as (1) postoperative systolic blood pressure ≥180 mm Hg and an increase of systolic blood pressure ≥35 mm Hg above preoperative baselines or (2) diastolic blood pressure >100 mg Hg and an increase >20 mm Hg or (3) any elevated blood pressure necessitating intravenous nitroprusside or other additional parenteral antihypertensive medications during the first 24 hours after surgery. This postoperative period included the time in the operating room and the time in the recovery room. Blood pressure measurements were recorded on a continuous basis by intraarterial line monitors and were considered elevated if the blood pressures met the above criteria for at least 5 minutes after carotid endarterectomy. The arterial line measurements were adjusted to correlated with the patient's most accurate pressure method established before surgery (i.e., cuff vs doppler; right vs left arm).

Surgical techniques. The participating surgeons from the Vascular Surgery Section at the UCLA Center for the Health Sciences performed each carotid endarterectomy according to their accustomed standard surgical techniques. In addition, on identifying and dissecting free the internal jugular vein from the carotid artery, the surgeon inserted percutaneously but with direct vision a standard 16-gauge, 8-inch flexible polyurethane intravenous catheter through a 14-gauge needle into the internal jugular vein. This catheter was guided in a cranial direction and the catheter tip was positioned at the base of the skull between the mastoid and the styloid processes. The common facial vein was ligated and divided to remove most of the facial venous effluence. This internal jugular vein catheter was then left in place for subsequent blood sampling. The catheter was secured in place and kept open by a constant infusion of D_5W with 1000 U heparin/L at 25 ml/hr. The catheter was removed the following morning, 18 to 24 hours after carotid endarterectomy. Although there were no complications from the catheter insertion or removal, several of the catheters became nonfunctional prematurely and thus were removed before all blood samples were obtained. Thus not all

patients had a complete set of blood samples (i.e., samples I to IV). However, all patients had a preoperative and at least one postoperative sample. Those patients lacking a preoperative and at least one postoperative sample were excluded from the study.

Collection and processing of blood samples. Blood samples were drawn from the peripheral arterial catheter (peripheral samples) and the internal jugular vein catheter (cranial samples) at the following times: (1) immediately after insertion of the internal jugular vein catheter before carotid clamping (sample I, baseline); (2) immediately after carotid cross-clamp release (sample II); (3) 2 to 6 hours after surgery (sample III) (this sample was drawn during the time the patient became hypertensive or the sample was drawn at the end of the 6-hour period if the patient did not develop postoperative hypertension); and (4) 18 to 24 hours after surgery, just before removal of the jugular and arterial line catheters (sample IV). For each blood sample determination, 30 ml from the internal jugular vein and 30 ml from the peripheral artery were drawn into 35 ml syringes and transferred immediately into iced EDTA glass tubes. Within 30 minutes of collection, the iced samples were spun in a refrigerated centrifuge and the plasma was decanted and stored at $-80°$ C until testing. Testing was performed within 6 months of collection in groups of eight to 10 patients.

Renin and catecholamine assays. Renin concentrations were determined by a radioimmunoassay described by Cohen et al.[22] The renin assays were run by two different independent contractors to verify the validity of the data. The catecholamine assays were determined by high-performance liquid chromatography by the UCLA clinical laboratories.[23] These determinations were tested in duplicate for verification of the data. The accuracy of the renin and catecholamine assays has been reported to be 95% for these laboratories. Because of refrigeration failure, some of the blood samples were unsuitable for testing. Thus reliable renin determinations were available in the first 45 of the 47 study cases and catecholamine determinations were available in the last 37.

Data analysis. Data analysis was performed by the Student *t* test.

RESULTS

Patient data. The 47 study cases involved 22 men and 25 women. The average age was 69.2 years (range 52 to 86 years). The indications for surgery are outlined in Table I. Nineteen patients were symp-

Table II. Postoperative antihypertensive medications

	PCEH (n = 29)		No PCEH (n = 18)	
	No.	%	No.	%
Nitroprusside	21	72	0	
Nitrosamines	13	45	4	22
β-blockers	8	28	4	22
Calcium channel blockers	6	21	2	11
Captopril (parenteral)	4	14	0	
α-blockers	3	10	0	
Clonidine	1	3	0	
Aldomet	1	3	1	6
None	0		11	61

PCEH, Postcarotid endarterectomy hypertension.

tom free, 11 had amaurosis fugax, 12 had had transient ischemic attacks, and five had had a stroke.

Perioperative factors that potentially could influence the occurrence of post-carotid endarterectomy hypertension are listed in Table I. Preoperative hypertension was present in 24 of the 47 patients. Thirty-six cases involved an ipsilateral high-grade carotid stenosis. Nineteen patients had abnormal preoperative neurologic examinations. Nine patients had diabetes mellitus. During surgery a carotid shunt was used in 27 of the 47 cases. Isoflurane anesthetic was used in 24 cases. A balanced nitrous narcotic anesthetic was used in the other 23 cases. Six of the 47 patients exhibited a new postoperative neurologic deficit. All six deficits were transient and resolved within 24 to 48 hours. There were no frank strokes in this group of patients.

Post-carotid endarterectomy hypertension occurred in 29 of the 47 patients (62%). The antihypertensive medications received in the early postoperative period by these patients are listed in Table II. Twenty-one of the 29 patients (72%) who had postoperative hypertension received intravenous nitroprusside. Approximately half of the hypertensive patients also received various intravenous, parenteral, or topical nitrosamines. A minority of the patients received β-blockers, calcium channel blockers, α-blockers, and other miscellaneous antihypertensive medications. Most of the hypertensive patients who did not receive intravenous nitroprusside received a combination of the other antihypertensive medications rather than a single agent. The one exception was a patient who received clonidine alone.

Among the 15 patients who did not exhibit postoperative hypertension, only a minority of patients received antihypertensive medications. These medications almost uniformly involved nitrosamines and

Table III. Ratio of norepinephrine values over baseline (sample I)

		n	No PCEH	n	PCEH	p Value
Sample II (after carotid clamp release)	Cranial	14	0.97 ± 0.36	18	1.40 ± 0.74	0.032
	Peripheral	15	0.97 ± 0.31	17	1.40 ± 0.75	0.101
Sample III (2-6 hr postoperative)	Cranial	10	0.90 ± 0.48	15	2.24 ± 1.94	0.005
	Peripheral	11	1.21 ± 1.05	15	2.26 ± 2.72	0.064
Sample IV (18-24 hr postoperative)	Cranial	6	1.41 ± 0.83	10	2.37 ± 2.15	NS
	Peripheral	8	1.51 ± 0.60	8	3.42 ± 3.01	0.090

PCEH, Postcarotid endarterectomy hypertension.

Table IV. Ratio of epinephrine values over baseline (sample I)

		n	No PCEH	n	PCEH	p Value
Sample II (After carotid clamp release)	Cranial	16	1.26 ± 0.71	27	1.14 ± 0.54	NS
	Peripheral	15	1.21 ± 1.50	17	1.50 ± 0.97	NS
Sample III (2-6 hr postoperative)	Cranial	8	2.68 ± 2.58	15	6.82 ± 9.73	NS
	Peripheral	9	2.36 ± 2.18	15	5.94 ± 7.64	NS
Sample IV (18-24 hr postoperative)	Cranial	6	2.51 ± 1.63	10	3.97 ± 4.83	NS
	Peripheral	6	2.14 ± 1.44	8	5.27 ± 5.72	NS

PCEH, Postcarotid endarterectomy hypertension.

Table V. Ratio of dopamine values over baseline (sample I)

		n	No PCEH	n	PCEH	p Value
Sample II (After carotid clamp release)	Cranial	13	1.09 ± 0.31	18	1.56 ± 1.18	NS
	Peripheral	14	1.37 ± 0.64	17	1.44 ± 0.92	NS
Sample III (2-6 hr postoperative)	Cranial	8	1.18 ± 0.49	15	1.62 ± 0.49	NS
	Peripheral	9	1.18 ± 0.51	15	1.69 ± 1.38	NS
Sample IV (18-24 hr postoperative)	Cranial	6	1.51 ± 0.85	10	1.25 ± 1.05	NS
	Peripheral	6	1.77 ± 0.93	8	1.74 ± 1.95	NS

PCEH, Postcarotid endarterectomy hypertension.

β-blockers, which were given primarily for cardiac reasons rather than hypertension. Only two patients in this group received medication strictly for blood pressure control, and these two patients received Aldomet and Tenormin, respectively, for their underlying preoperative hypertension. Eleven of the 18 nonhypertensive patients (61%) received no medications at all.

Catecholamine and renin data. The ratios of the norepinephrine values of samples II, III, and IV compared with sample I (the baseline value) are shown in Table III. The patients with post-carotid endarterectomy hypertension had a significantly higher ratio in cranial samples II and III ($p = 0.032$ and $p = 0.005$, respectively) than the patients without post-carotid endarterectomy hypertension. The peripheral ratios for samples II and III were also higher among the patients with post-carotid endarterectomy hypertension than in the patients without post-

carotid endarterectomy hypertension, but at a confidence level of only $p = 0.101$ and $p = 0.064$, respectively. At the 18 to 24-hour postoperative period, the cranial norepinephrine levels were generally back to baseline (p not significant), whereas the peripheral levels were still somewhat elevated($p = 0.09$).

Tables IV and V show the epinephrine and dopamine ratios, respectively. Although the patients with post-carotid endarterectomy hypertension tended to have higher ratios than the patients without post-carotid endarterectomy hypertension, the variability of the data reflected by the high standard deviation and the small number of samples erased any apparent differences between the two groups. The ratios of cranial to peripheral values for norepinephrine, epinephrine, and dopamine were also similar among the patients with and without post-carotid endarterectomy hypertension (Table VI).

The renin data shown in Tables VI and VII dem-

Table VI. Ratio of cranial to peripheral values

	Sample	n	No PCEH	n	PCEH	p Value
Norepinephrine	I	14	1.24 ± 0.56	17	1.15 ± 0.31	NS
	II	14	1.28 ± 0.93	19	1.22 ± 0.50	NS
	III	10	1.02 ± 0.35	16	1.19 ± 0.23	NS
	IV	6	0.99 ± 0.16	10	1.07 ± 0.10	NS
Epinephrine	I	14	0.99 ± 0.25	17	1.02 ± 0.17	NS
	II	14	1.02 ± 0.31	19	1.03 ± 0.42	NS
	III	10	1.01 ± 0.21	16	1.11 ± 0.49	NS
	IV	6	0.95 ± 0.29	10	0.99 ± 0.15	NS
Dopamine	I	14	0.96 ± 0.17	17	1.07 ± 0.31	NS
	II	14	0.82 ± 0.24	19	1.17 ± 0.69	NS
	III	10	0.94 ± 0.23	16	1.04 ± 0.19	NS
	IV	6	0.81 ± 0.26	10	1.13 ± 0.37	NS
Renin	I	15	1.11 ± 0.33	27	1.02 ± 0.31	NS
	II	16	1.16 ± 0.59	28	1.27 ± 0.58	NS
	III	9	1.08 ± 0.22	19	1.28 ± 0.89	NS
	IV	7	0.86 ± 0.15	11	0.98 ± 0.16	NS

PCEH, Postcarotid endarterectomy hypertension.

Table VII. Ratio of renin values over baseline (sample I)

		n	No PCEH	n	PCEH	p Value
Sample II (After carotid clamp release)	Cranial	16	1.26 ± 0.71	27	1.14 ± 0.54	NS
	Peripheral	15	1.27 ± 0.90	27	0.92 ± 0.36	NS
Sample III (2-6 hr postoperative)	Cranial	10	1.01 ± 0.64	17	1.18 ± 1.08	NS
	Peripheral	8	1.06 ± 0.63	21	0.80 ± 0.65	NS
Sample IV (18-24 hr postoperative)	Cranial	8	1.08 ± 1.30	11	1.03 ± 0.99	NS
	Peripheral	8	1.31 ± 0.77	12	1.29 ± 1.67	NS

PCEH, Postcarotid endarterectomy hypertension.

onstrated no significantly detectable difference between the patients with and those without post-carotid endarterectomy hypertension in any of the analyses. Thus there appears to be no correlation of postcarotid endarterectomy hypertension and renin activity. However, renin values were significantly higher in the cranial than the peripheral samples in sample II (cranial to peripheral ratio 1.23 ± 0.58; $p < 0.01$) and to a lesser degree in sample III (cranial to peripheral ratio 1.22 ± 0.74; $p = 0.13$), as seen in Table VIII. Because sample II represents the time period immediately after carotid cross-clamp release, this finding suggests that carotid clamping and release induced elevated cranial renin release. However, this increased cranial renin value did not correlate with the occurrence of post-carotid endarterectomy hypertension.

Table IX compares the mean cranial to peripheral ratios of baseline samples (sample I) for patients with and without preoperative hypertension. The group of patients with preoperative hypertension tended to have higher cranial to peripheral ratios for norepinephrine than the group of patients without pre-

operative hypertension. However, this difference was not statistically significant.

DISCUSSION

The distribution of age, sex, and indications for surgery were representative of the patients who generally undergo carotid endarterectomy at the UCLA Medical Center. The incidence of post-carotid endarterectomy hypertension in this study group was approximately 60%, which is similar to our previously reported incidence[24] but somewhat higher than most reported figures.[6-13,21] However, one should note that many of the study patients had multiple risk factors for developing post-carotid endarterectomy hypertension (i.e., preoperative hypertension, diabetes mellitus, tight carotid stenosis, and preoperative neurologic deficits).

Another reason for this high incidence may be that we used a less stringent criteria for post-carotid endarterectomy hypertension. Some investigators have used systolic blood pressure measurements >200 mm Hg for the criterion for hypertension.[3,6] Other investigators reported hypertension occurring

Table VIII. Comparison of cranial to peripheral values

	Sample	*n*	Cranial	*n*	Peripheral	Ratio C/P	*p Value*
Norepinephrine	I	32	319 ± 213	32	286 ± 207	1.2 ± 0.04	NS
	II	33	386 ± 360	34	353 ± 326	1.2 ± 0.7	NS
	III	26	462 ± 561	27	398 ± 436	1.1 ± 0.3	NS
	IV	17	419 ± 262	18	421 ± 255	1.0 ± 0.1	NS
Epinephrine	I	31	43 ± 60	31	43 ± 51	1.0 ± 0.2	NS
	II	32	39 ± 31	33	38 ± 28	1.0 ± 0.4	NS
	III	24	104 ± 115	25	91 ± 92	1.1 ± 0.4	NS
	IV	17	73 ± 58	16	79 ± 63	0.9 ± 0.2	NS
Dopamine	I	31	21 ± 9	31	20 ± 9	1.0 ± 0.3	NS
	II	32	28 ± 22	33	28 ± 17	1.0 ± 0.6	NS
	III	24	26 ± 18	25	26 ± 17	1.0 ± 0.2	NS
	IV	17	28 ± 31	16	28 ± 21	1.0 ± 0.4	NS
Renin	I	43	2.9 ± 2.9	43	3.2 ± 3.4	1.05 ± 0.32	NS
	II	45	2.9 ± 2.5	44	2.6 ± 2.2	1.23 ± 0.58	0.011
	III	29	2.2 ± 1.7	31	1.9 ± 1.8	1.22 ± 0.74	0.18
	IV	20	2.4 ± 2.9	22	2.5 ± 2.7	0.93 ± 0.16	NS

C, Cranial; P, peripheral.

Table IX. Mean cranial-to-peripheral ratio of baseline samples for patients with and without preoperative hypertension

	n	Preoperative HTN	*n*	No Preoperative HTN	*p Value*
Norepinephrine	14	1.34 ± 0.71	14	1.12 ± 0.26	NS
Epinephrine	14	0.98 ± 0.08	14	0.96 ± 0.22	NS
Dopamine	14	0.99 ± 0.10	14	0.98 ± 0.08	NS
Renin	21	1.08 ± 0.31	18	1.00 ± 0.37	NS

HTN, Hypertension.

only after the patient had reached the intensive care unit or the ward and did not count the hypertension that occurred in the immediate postoperative period.[6,21] However, we submit that our definition of post-carotid endarterectomy hypertension is reasonable because it represents blood pressure that occurred at the time the blood samples were drawn and, more importantly, represents blood pressure that required treatment. We generally attempt to keep systolic blood pressures <180 mm Hg pressure and diastolic <100 mm Hg pressure. For future studies, investigators in this field should adopt a uniform definition of post-carotid endarterectomy hypertension.

Most patients who developed post-carotid endarterectomy hypertension received intravenous nitroprusside or intravenous nitroglycerin (Table II). Those who did not receive these medications almost always received a combination of multiple medications such as a β-blocker, calcium channel blocker, or α-blocker. Most patients who did not develop post-carotid endarterectomy hypertension did not receive any antihypertensive medications. It is conceivable that these drugs could influence the level of

the catechcolamine and renin activity. For example, propranolol blocks peripheral release of renin[19] and, therefore, could cause the relatively decreased peripheral renin values seen in samples II and III (Table VIII). However, this explanation alone is inadequate because samples I and IV had cranial and peripheral renin levels that were similar to each other. Clearly the carotid cross-clamping or release was temporally related to the change in the cranial renin value. Hypotension from any cause (i.e., overmedication, hypovolemia, and even postural changes alone) can lead to increased renin and catecholamine release.[20,25] However, all patients in this study were well hydrated, patients were uniformly kept at bed rest with the head elevated at 30 degrees during the first 18 to 24 hours after surgery, and no patient became hypotensive in the postoperative period. Elevated catecholamine levels could also result from postoperative pain.[20] However, many of these patients received a bupevacaine hydrochloride (Marcaine) block of the incision site to control the pain and most patients generally had minimal pain that was well controlled with mild analgesics.

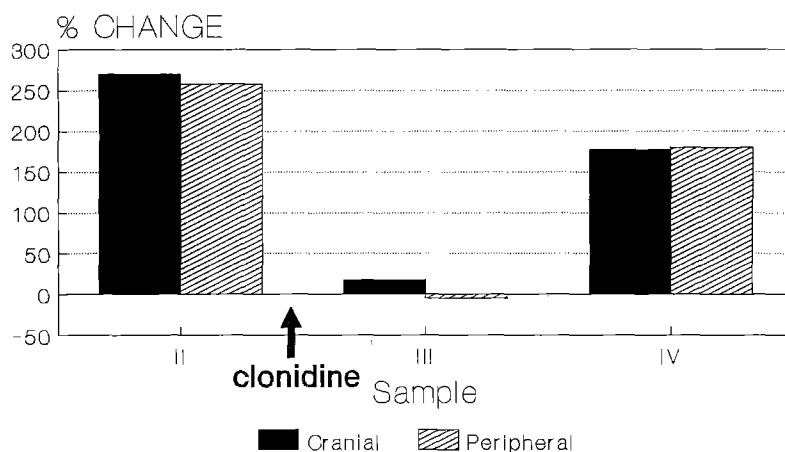The norepinephrine elevations after carotid end-

Fig. 1. Norepinephrine treatment for postcarotid endarterectomy hypertension (patient 25).

arterectomy in patients who developed post-carotid ndarterectomy hypertension hypertension support the findings reported by Moore and Hall.[17] Moore and Hall found that nephrectomy did not block this hypertensive response, yet total epidural anesthesia did. This phenomenon suggests that a sympathetic-mediated system is involved in the cause of post-carotid endarterectomy hypertension. Our data suggest that the norepinephrine is a factor and, furthermore, is cranial in origin.

The exact source of the cranial norepinephrine responsible for post-carotid endarterectomy hypertension is not known. The increased norepinephrine values found in the internal jugular vein near the cavernous sinus suggest a cerebral source. One possible source is the cerebral vessels whose blood brain barrier has become disrupted by cerebral hyperperfusion after carotid endarterectomy.[26] Another possible site is the brain stem, which is a well-established site of norepinephrine production.[27,28] Norepinephrine from this site could also result in increased peripheral norepinephrine levels through the spinal cord and this hypertensive effect could be blocked by total epidural anesthesia, as reported by Moore and Hall.[17] Furthermore, this spinal cord stimulation of norepinephrine release could explain why the peripheral norepinephrine levels rise parallel to the cranial values, although in a smaller amount (Table III).

In a normal resting human, the peripheral norepinephrine level is lower in the venous than in the arterial circulation, because the distal end plates of the peripheral arterial and capillary beds are not releasing norepinephrine in a significant amount.[29] However, in a nonresting or hypotensive patient, norepinephrine is released at the regional peripheral capillary and arterial end plates, leading to increased

venous norepinephrine values and thus an increased venous-to-arterial ratio. The increased jugular norepinephrine levels compared with arterial levels found in this study suggest that the same phenomenon may be occurring in the cranial circulation. One can postulate that the cranial sympathetic system, similar to the peripheral system, releases norepinephrine at the capillary or blood brain barrier level in response to hypoperfusion during carotid clamping. This hypoperfusion could also occur in the intermediate postoperative period if the patient develops subclinical cerebral edema and increased intracranial pressure. Thus transient disruption of the blood brain barrier induced by subclinical or frank ischemia could lead to increased norepinephrine release into the jugular vein and the subsequent post-carotid endarterectomy hypertension.

Renin activity did not appear to correlate with post-carotid endarterectomy hypertension, even when the data were analyzed in the same fashion reported by Smith,[21] that is, when the cranial-to-peripheral ratios were analyzed (Table VI). However, our data still support Smith's data and conclusion that renin is released from the cerebral circulation into the internal jugular vein after carotid clamping. Table VIII reveals elevated cranial renin values compared with peripheral values in samples II and III (i.e., when the carotid clamp has been applied and then released). Like norepinephrine, renin activity should also be lower in the internal jugular vein system than in the radial artery in a normal person, as described previously, because renin has a very short half-life of approximately 2 minutes and is released from the kidneys directly into the inferior vena cava. Thus increased cranial renin activity after carotid clamping suggests a cranial source of renin release.

Perhaps a Goldblatt phenomenon occurs in the central nervous system circulation. Certainly there is abundant evidence in the literature suggesting that animals possess a separate renin angiotensin system within the central nervous system, specifically on the blood side of the blood brain barrier.[30-33] Although this system has not been confirmed in humans, our data, as well as Smith's data, suggest that humans also have a central nervous system renin angiotensin system independent of the renal system. However, the role of this system in the development of post-carotid endarterectomy hypertension is not clear. Our data suggest that the elevated cranial renin value is overwhelmed by the cranial sympathetic nervous system, making the renin angiotensin system a secondary minor component of post-carotid endarterectomy hypertension. In fact, four of our hypertensive patients received parenteral captopril, an angiotensin converting enzyme inhibitor, and the results were mixed. Two patients responded to captopril and two did not. The other possibility is that intracranial renin is in the form of an inactive isomer as demonstrated in pigs.[32]

Our data suggest that treatment of post-carotid endarterectomy hypertension should include a central-acting sympatholytic agent. A prime example of such a medication is clonidine, which inhibits central sympathetic outflow and thereby reduces peripheral (and perhaps cranial) plasma norepinephrine levels.[34,35] In fact, one patient received only clonidine for his post-carotid endarterectomy hypertension, as shown in Fig. 1. It is interesting to note that the cranial and peripheral catecholamine values were significantly elevated compared with baseline at sample time II when the patient was quite hypertensive. After the patient received clonidine there was an immediate reduction in the blood pressure, as well as the cranial and peripheral norepinephrine levels. Then at the fourth time sample (i.e., 18 to 24 hours after surgery), after the clonidine had worn off, the patient's blood pressure had begun to creep upward and the cranial and peripheral norepinephrine levels likewise began to increase again. Although this is only an anecdotal observation, it is consistent with the data found in this study. Perhaps a trial of routine perioperative clonidine should be given to patients undergoing carotid endarterectomy to verify this observation.

Our finding that cranial norepinephrine may be important in the pathogenesis of post-carotid endarterectomy hypertension raises the distinct possibility that other forms of hypertension such as essential hypertension may involve the central nervous

system more than is currently appreciated. One should note that many of the sample I baseline values for norepinephrine were higher in the cranial than the peripheral samples. This observation was particularly noteworthy among the patients who had preoperative hypertension, although this trend was not statistically significant because of the small numbers (Table IX). This finding suggests that the patients with peoperative hypertension had underlying increased production of cranial norepinephrine. It is possible that patients with preoperative hypertension have subclinical or chronic cerebral ischemia leading to a hyperactive intracranial sympathetic system, as suggested by Guyton[36] in 1948. Further investigations in this area are indicated.

In conclusion, post-carotid endarterectomy hypertension is associated with elevated cranial and peripheral norepinephrine values. There is a stronger association of post-carotid endarterectomy hypertension with cranial than with peripheral norepinephrine. This observation suggests that post-carotid endarterectomy hypertension is mediated by a central nervous system sympathomimetic mechanism. An intracranial renin angiotensin system probably exists but does not appear to influence post-carotid endarterectomy hypertension significantly. Thus optimal treatment and prevention of post-carotid endarterectomy hypertension should include a central-acting sympatholytic agent.

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DISCUSSION

Dr. Jonathan B. Towne (Milwaukee, Wis.). I have always felt that the cause of hypertension after carotid endarterectomy was the result of an intracerebral mechanism. This work suggests that the brain releases norepinephrine, which mediates postoperative hypertension. I wonder if defining postoperative hypertension as blood pressure >180 mm Hg for at least 5 minutes was too sensitive an indicator in this group of patients with atherosclerosis who

are taking a variety of cardiac and vasoactive medications and when two different anesthetic techniques were used.

Was there a correlation between norepinephrine levels and the degree and duration of the postoperative hypertension? Also, was there a correlation between these levels and the occurrence of neurologic deficits in the postoperative period? Were norepinephrine levels correlated with either stump pressure or pressure obtained before surgery with Gee-OPG studies?

I was intrigued that the levels of epinephrine and norepinephrine were higher 24 hours after surgery than they were in the immediate postendarterectomy period, because my interpretation of the study was that the hypothesis was that carotid clamping was the cause of the norepinephrine release, since we know that the half-life of norepinephrine in the body is in terms of minutes. Do you have any explanation of this finding?

There is no mention made of controls. Do you have any data as to the intracerebral production of norepinephrine in patients undergoing similar surgical procedures? For example, did you evaluate patients for the effects of anesthesia, as well as obtain studies on patients who had undergone nonvascular carotid procedures (e.g., thyroidectomy)?

Dr. Ahn (closing). We did look at all those factors that Dr. Towne mentioned (i.e., the degree of stenosis, stump pressure, neurologic deficits, etc.) and tried to determine whether there was any relationship to the catecholamine levels. However, the sample size, 47 cases, was too small to allow any statistically significant conclusions. We did not include this analysis in our article for fear that one might draw false conclusions from such a small sample size. What I can tell you is that for the group collectively, the indications for surgery were amaurosis fugax (23% of the patients), transient ischemic attacks (26%), stroke (11%), and asymptomatic factors (40%). The incidence of risk factors for post-carotid endarterectomy hypertension were preoperative hypertension (51% of patients), diabetes mellitus(19%), tight carotid stenosis (>75%)(77%), abnormal preoperative neurologic examination (40%), use of isoflurane anesthetic (51%), carotid shunts (57%), and new postoperative neurologic deficits (all transient) (13%). Basically the incidence of these risk factors is representative of patients undergoing carotid endarterectomy as reported previously from the University of California, Los Angeles, and others.

In regard to Dr. Towne's question about why there was such a high postoperative norepinephrine level at 24 hours, I can only guess. One possible explanation is that the patient is up and about and is not in a quiet supine position. We know that in a normal, resting, quiet position the norepinephrine levels are low. However, as soon as one stands up, moves around, or gets stimulated, the norepinephrine level increases. Even with this increase, however, there was no association of the 24-hour catecholamine level and the occurrence of post-carotid endarterectomy hypertension. Furthermore, there was no statistically elevated increased cranial-to-peripheral catecholamine ratio in the samples drawn 24 hours after surgery. Thus I suspect that the 24-hour sample reflects the patient's baseline normal activity.

Dr. Towne mentioned that we did not have any controls, and he is correct to an extent. We have not done the same experiment in patients who undergo peripheral vascular operations or general surgery operations. So I cannot answer the question of what surgery does or what anesthesia does to the intracranial catecholamine levels. However, there are articles in the literature studying catecholamine levels in normal humans, and these studies certainly show that the relationship that we saw in our study: that is, the elevated cranial-to-peripheral norepinephrine levels do not occur in normal human control subjects.

I should also mention that if you look at sample I, our baseline sample that is our control for this particular study the way it was designed, there was no association of the sample I values and post-carotid endarterectomy hypertension. Furthermore, sample I cranial catecholamine levels were no higher than the peripheral levels. So I would conclude that the elevated cranial norepinephrine levels increased only after carotid clamping, that is, in samples II and III in patients with post-carotid endarterectomy hypertension. Thus as the data stand, I submit that post-carotid endarterectomy hypertension is associated with elevated intracranial norepinephrine levels.