

Reversal of Severe Cerebral Vasospasm in Three Patients after Aneurysmal Subarachnoid Hemorrhage: Initial Observations Regarding the Use of Intraventricular Sodium Nitroprusside in Humans

Jeffrey E. Thomas, M.D., Robert H. Rosenwasser, M.D.

Division of Cerebrovascular Surgery and Interventional Neuroradiology, Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania

OBJECTIVE AND IMPORTANCE: The chronic delayed type of cerebral vasoconstriction that occurs after aneurysmal subarachnoid hemorrhage (SAH) is now the most important cause of mortality and neurological morbidity for patients who initially survive the rupture of cerebral aneurysms. Although intravascular volume expansion and cardiac performance enhancement have had a profound impact on the treatment of the chronic delayed type of cerebral vasoconstriction, this form of treatment is not tolerated by all patients and is unhelpful in some. A more specific and more reliable treatment for this condition has not been previously reported. Previous work in an animal model has demonstrated the efficacy of nitric oxide-donating compounds in reversing severe cerebral vasoconstriction when delivered to the adventitial side of the blood vessel. A clinical study was initiated after receiving approval from the United States Food and Drug Administration and the institutional review board.

CLINICAL PRESENTATION: Three cases of prompt and substantial reversal of medically refractory vasospasm occurring after aneurysmal SAH in humans using an intrathecally administered nitric oxide donor and clinical, angiographic, and ultrasonographic documentation are presented. All patients developed severe vasospasm refractory to medical treatment 5 to 12 days after sustaining aneurysmal SAH. All patients manifested stupor of new onset (Glasgow Coma Scale score of 7) and new focal neurological deficit (hemiplegia). The condition was angiographically demonstrated in all cases.

INTERVENTION: The patients were treated with intrathecally administered sodium nitroprusside, which caused the reversal of vasospasm, which was documented by angiography and transcranial Doppler ultrasonography up to 54 hours later and also by dramatic clinical improvement. Complications related to intracranial pressure elevation, changes in vital signs, and hemodynamic parameters were not observed during or after the procedures. Radiographic evidence of the reversal of vasospasm and brain ischemia was obtained. The clinical outcomes of the treated patients were excellent. All patients presented with hemiplegia and stupor that resolved or markedly improved (within several days, two patients; within 12 hours, one patient). All three patients were discharged and were living at home at the time of manuscript submission.

CONCLUSION: These preliminary observations suggest that sodium nitroprusside delivered by an intrathecal route of administration may be a useful treatment for severe vasospasm complicating SAH in humans.

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Key words: Angiography, Human, Intrathecal, Nitric oxide, Treatment, Vasospasm

A reliably effective treatment for the chronic delayed type of cerebral vasoconstriction (CDCV) that occurs after aneurysmal subarachnoid hemorrhage (SAH) remains elusive. The mainstay of treatment for this complication, now the most important cause of mortality and neurological morbidity after aneurysmal SAH, is hypertensive,

hypervolemic, hemodilution (HHH) therapy. Because severe cases of CDCV may be refractory to HHH therapy and because some patients may not tolerate HHH therapy for medical reasons, an alternative treatment for CDCV is desirable. Three cases of the prompt and substantial reversal of medically refractory CDCV using an intrathecally administered

nitric oxide (NO) donor and angiographic and ultrasonographic documentation are presented. The effects of this treatment were still angiographically and clinically evident more than 2 days after treatment. Changes in intracranial pressure (ICP), vital signs, and hemodynamic parameters were minimal or nonexistent. Radiographic evidence of the reversal of vasospasm and brain ischemia, by angiography, transcranial Doppler (TCD) ultrasonography, and computed tomography (CT), was obtained. These preliminary observations suggest that NO donors delivered by an intrathecal or adventitial route of administration may be a useful treatment for severe CDCV in humans.

PATIENTS AND METHODS

Approval and informed consent

Approval of this investigation from the institutional review board (Thomas Jefferson University, Jefferson Medical College, IRB Control No. 97.9035) and the Food and Drug Administration under the Investigational New Drug Treatment protocol (FDA IND No. 52307, 1997) was obtained by the principal investigator (JET), and informed consent was obtained from each patient's immediate family. Informed consent was obtained in advance (at admission) whenever possible for every patient diagnosed with aneurysmal SAH.

Inclusion and exclusion criteria

Patients eligible for treatment were patients with symptomatic aneurysmal SAH-induced CDCV refractory to HHH therapy for 1 hour. TCD velocity measurements (carotid index) were used to diagnose CDCV in the context of the clinical examination, and asymptomatic patients were not considered for treatment. For patients for whom the clinical examination was not available (e.g., those patients under pentobarbital-induced electroencephalographic burst suppression for brain protection), a higher reliance was placed on TCD measurements, although other criteria were also used (increase in ICP or volume of cerebrospinal fluid [CSF] drainage for a given parameter per hour). In addition to asymptomatic patients, patients with obvious infarction or intraparenchymal hematoma revealed by CT, patients with ICP not reducible below 20 mm Hg, and patients younger than 18 years were excluded from participation in this study.

TCD measurements

TCD velocity measurements were obtained by a single operator who was specifically trained in the technique. The values were normalized for varying hemodynamic conditions by using the carotid index (mean middle cerebral artery [MCA] velocity/mean cervical internal carotid artery [ICA] velocity).

Angiography

Cerebral angiography was performed in the standard manner (transfemoral selective) before, during, and after treatment with sodium nitroprusside (SNP), using a high-resolution biplane digital subtraction technique. In two of the patients (Patients 1 and 2), additional post-treatment angiography was performed between 12 and 54 hours after treatment. Cerebral circulation times, defined as the interval in seconds between the first observed filling of the ipsilateral carotid siphon and the first observed filling of either transverse sinus on the anteroposterior angiogram, were estimated to the nearest half-second and determined by a single observer. All cerebral circulation times were measured at constant mean arterial blood pressure (MABP). Blood vessel diameters were measured digitally, using the computer paradigm of the Phillips Integris 3000 Biplane Digital Subtraction Angiography Unit (Gensia Pharmaceuticals, Irvine, CA), by a single observer using constant anatomic references from the angiogram, such as bony landmarks or origins of readily observed branch vessels.

Dosage and administration

All SNP was administered via ventriculostomy, which was performed in the standard manner (cannulation of the lateral ventricle via the frontal lobe). SNP was delivered as a solution in the patient's own CSF, at concentrations between 1 and 4 mg/ml. The initial dosage range of the intrathecally administered SNP (ITSNP) was based on previous experimental observations (10) and the clinical response as measured by intraprocedural monitoring and angiography (see text). Dosage was limited to 30 mg per procedure in accordance with the structure of a dose escalation study in progress.

CLINICAL PRESENTATION

Patient 1

A 42-year-old woman sustained a Hunt and Hess (2) Grade III SAH that resulted from the rupture of a left-sided ICA bifurcation aneurysm. She underwent an uncomplicated craniotomy and clip ligation of the aneurysm within 24 hours of SAH at an outside institution. On the 5th day after SAH, she was noted to have a deterioration in mental status and right-sided weakness (Glasgow Coma Scale [GCS] score of 7) (8), which progressed to hemiplegia before she was transferred to our institution. The patient's condition failed to improve after transfer, despite the initiation of HHH therapy and cardiac performance enhancement with optimization of pulmonary capillary wedge pressure, MABP, and cardiac index as determined by Swan-Ganz catheterization. CT demonstrated low attenuation areas of left and right cerebral cortex in anterior cerebral (right) and anterior and middle carotid (left) arterial territory distributions, consistent with ischemia. Cerebral angiography performed 1 hour after the initiation of aggressive HHH therapy disclosed severe vasoconstriction of the anterior circulation vessels bilaterally, including the proximal and distal anterior cerebral artery (ACA) and posterior communicating artery (PComA) on the right and the proximal ACA and proximal and distal

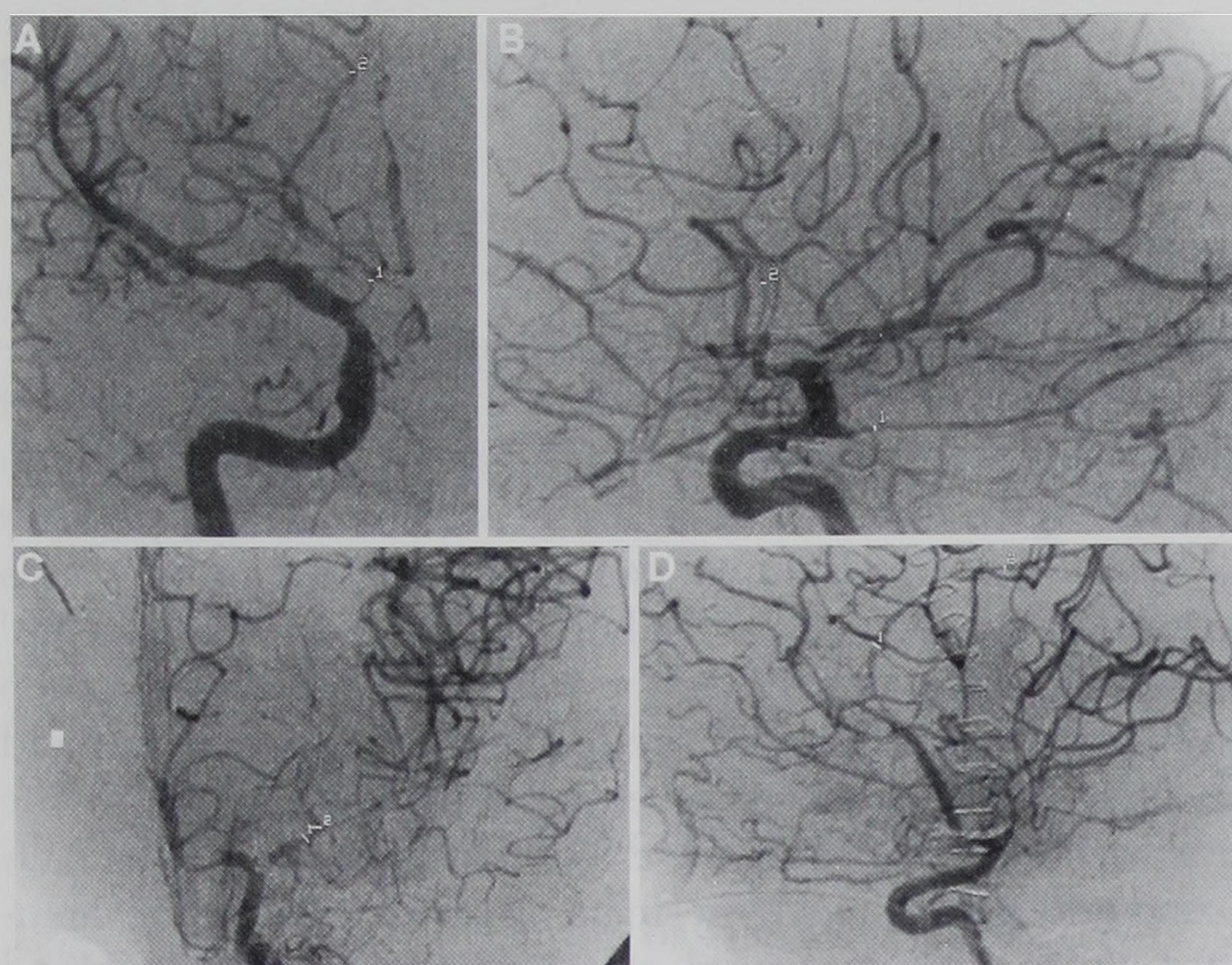


FIGURE 1. Patient 1. *A*, anteroposterior projection angiogram of the right cerebral ICA, obtained before treatment. Note that the A1 segment of the ACA is severely constricted, as is the PComA (1); distal PCom artery (2). *B*, lateral projection angiogram of the right cerebral ICA, obtained before treatment. Note that the PComA (1) is severely constricted; the A2 artery segment (2). *C*, anteroposterior projection angiogram of the left cerebral ICA, obtained before treatment. Note that the A1 and A3 segments of the ACA and the M1 (1) and M2 segments of the MCA (2) are severely constricted. *D*, lateral projection angiogram of the left cerebral ICA, obtained before treatment. The degree of vasospasm in the A3 (1) segment of the ACA (2) is apparent.

MCA on the left (Fig. 1, *A–D*). Left- and right-sided cerebral circulation times were 7 and 7.5 seconds, respectively. Control angiograms from the left ICA were obtained at 15-minute intervals, while a solution of SNP (1.0 mg/ml) was delivered via ventriculostomy into the right lateral ventricle in 5.0-ml aliquots. Immediately before injection, a volume of CSF equal to or slightly greater than the injected volume was withdrawn from the ventriculostomy. ICP monitoring and continuous hemodynamic monitoring (MABP, Swan-Ganz intracardiac catheter) and neurophysiological monitoring (electroencephalography, somatosensory evoked potentials [SSEPs]) were performed simultaneously. A total dose of 30 mg of ITSNP was administered.

Results

A progressive and marked increase in the caliber of multiple previously constricted vessels was observed, beginning with the 30-minute angiography. There was no significant change in MABP, ICP, or neurophysiological monitoring parameters from the baseline during or after treatment (Table 1). TCD velocity measurements obtained after the procedure were within normal limits, with the exception of those of the left MCA, which were initially normal postprocedure and became moderately elevated (mean velocity, <200 cm/s) 20 hours after the procedure. TCD measurements remained unchanged from these values 26 hours after the procedure (Table 2). A control cerebral angiogram obtained 24 hours after treatment demonstrated persistent substantial dilation of the previously spastic vessels on the right (A1, PComA) and significant further increase in the dilation of those on the left (M1, M2, A1, A2), according to digital measurements (Fig. 2, *A–D*); enhanced distal circulation was present (Fig. 2, *E* and *F*). The resulting percentage change from the baseline calibers of these

TABLE 1. Measurement of Mean Arterial Blood Pressure and Intracranial Pressure for Patient 1 during Treatment with Intrathecally Administered Sodium Nitroprusside^a

Time of dose (min)	0	30	60	90	120	140
MABP (mm Hg)	125	114	122	110	110	123
ICP (mm Hg)	7	7	7	7	7	9

^a MABP, mean arterial blood pressure; ICP, intracranial blood pressure. Measurements of MABP and ICP for Patient 1, obtained continuously and recorded at times of administration of intraventricular sodium nitroprusside (see text), are shown. Entire treatment duration was 2 hours 20 minutes.

vessels ranged from 90 to 115% (mean, 104%) for the right and from 26 to 132% (mean, 98%) for the left (Table 3). The cerebral circulation time was reduced to 5 seconds for both hemispheres. CT of the brain performed 48 hours after treatment showed improvement in the low attenuation regions. Cerebral angiography was repeated at 54 hours after treatment because of increased TCD velocities measured in the left M1. The dilated appearance of the right-sided vessels and the left-sided A1 and A2 persisted, whereas a small degree of focal narrowing was observed in the left M1 and proximal M2. The left M1 underwent angioplasty 54 hours after the SNP treatment because the constricted segment was unique and proximal, and its caliber was restored to that produced by SNP treatment. The patient subsequently achieved a dramatic clinical recovery. She emerged from coma and within several days began to demonstrate useful function of the previously plegic right side (the leg more than the arm). Serum cyanate levels drawn on the evening after treatment were undetectable. She was discharged to a rehabilitation facility within 2 weeks in stable condition, with a GCS score of 15. At post-treatment Day 129, she was able to walk with the aid of a walker at home, able to feed herself, and able to converse, with a moderate pure motor dysphasia. Her right upper extremity remained densely paretic, although she was able to move it willfully.

Patient 2

A 50-year-old man presented with a clinical (2) Grade III and radiographic (1) Grade III SAH that resulted from a ruptured right-sided MCA aneurysm. His medical history was significant for poorly controlled arterial hypertension and a 50 pack-year history of cigarette smoking. The patient underwent an uncomplicated right pterional craniotomy and clip ligation of the aneurysm on hospital Day 2 (post-SAH Day 1). The surgery was remarkable for an extremely swollen, injected-appearing brain with copious SAH despite effective osmotic diuresis and ventricular drainage. The temporary occlusion time of the inferior division of the right MCA was 5 minutes under etomidate burst suppression anesthesia. No changes in neurophysiological monitoring parameters (electroencephalography, SSEPs) were observed during the operation. The bone plate was not replaced at the termination of the operation in anticipation of cerebral swelling. The patient awakened uneventfully, however, and was extubated the day after surgery. He had no demonstrable focal neurological deficit for 5 days, and his GCS score was consistently 14 to 15. On postoperative Day 5 (SAH Day 6), the patient manifested an aggravated increase in TCD velocities on the left (Table 4) simultaneously with a profound depression in mental status (GCS score of 7) and failure to move the right side of his body. He was emergently intubated. CT of the brain demonstrated right-sided cerebral swelling, moderate ventriculomegaly relative to the computed tomographic scan obtained at admission, and persistent residual SAH. No focal injury to the left cerebral hemisphere was radiographically discernible. A ventriculos-

TABLE 2. Mean Transcranial Doppler Velocities and Calculated Velocity Indices of Patient 1 after Treatment with Intraventricular Sodium Nitroprusside^a

Vessel/Index	Hours after Treatment										Days after Treatment			
	1	4	20	26	46	51	70.5	75	95	100	120	16	17	18
RMCA	71	73	85	93	113	107	100	100	135	140	136	82	97	97
RACA	162	50	47	54	73	73	57	71	143	143	112	93	128	78
RICA	31	36	44	44	29	28	62	52	73	67	56	50	47	NM
RCIX ^b	2.29	2.03	1.93	2.11	3.90	3.82	1.61	1.92	1.85	2.09	2.43	1.64	2.06	NM
LMCA	73	76	170	169	230	230	128	145	162	181	188	123	143	132
LACA	42	59	82	59	128	129	54	82	85	92	90	42	100	69
LICA	38	31	33	32	41	42	57	35	38	40	46	38	40	38
LCIX ^b	1.92	2.45	5.15	5.28	5.61	5.48	2.25	4.14	4.26	4.53	4.09	3.24	3.58	3.47
AComA	45	54	57	42	100	54	53	107	162	138	97	90	100	NM

^a RMCA, right middle cerebral artery; RACA, right anterior cerebral artery; RICA, right internal carotid artery; RCIX, right carotid index; LMCA, left middle cerebral artery; LACA, left anterior cerebral artery; LICA, left internal carotid artery; LCIX, left carotid index; ACoA, anterior communicating artery; NM, not measured. Mean transcranial Doppler velocities of the cerebral arteries of Patient 1, measured after treatment with intraventricular sodium nitroprusside (in cm/s), are shown. No measurements were obtained before treatment, because the patient was received in transfer in extremis.

^b Carotid index was calculated as follows: mean MCA velocity/mean cervical ICA velocity.

tomy was placed for ventricular decompression. The ICP remained between 15 and 18 mm Hg. No significant improvement in the patient's neurological status was observed after 1 hour, despite optimization of HHH therapy. The patient was taken emergently for cerebral angiography, which demonstrated severe narrowing of the right A1, left A1, and left M1 arterial segments (Fig. 3, A-C). The cerebral circulation time was 8 seconds on the left and 6.5 seconds on the right. Prolonged SSEP latencies representing the right upper and lower extremities observed at baseline before intervention were thought to be consistent with the angiographic demonstration of vasospasm in the left MCA and ACA distribution (Fig. 4). ITSNP (4.0 mg/ml) was delivered in aliquots of 1.0 ml, admixed with the patient's own CSF from the ventriculostomy, by means of a closed system using two syringes at intervals of 5 to 10 minutes for 53 minutes. The first dose was exceptional in that 2.0 ml (8.0 mg) was administered and 20 minutes were allowed to elapse before administration of the second dose (Table 5). The total dose delivered was 30 mg. The circumstances of administration in terms of neuroanesthetic and neurophysiological monitoring were identical to those for Patient 1.

Results

Improvement in the previously prolonged latencies of the left cortical SSEPs was observed within 23 minutes of the administration of SNP, dropping from 23.9 to 20.0 milliseconds for the upper extremity and from 51.5 to 47.7 milliseconds for the lower extremity (Fig. 4). No significant change in the caliber of the larger conductance vessels (left A1 and M1) was observed at first, and concurrent cerebral angioplasty was attempted. Because of remarkable tortuosity of the patient's left ICA, the balloon catheter could not be navigated beyond the carotid siphon. SNP administration continued, and progressive dilation of M1 became apparent. Although administration was stopped at 30 mg, angiographic improvement continued, and therefore, no further attempt to perform angioplasty was made. The left-sided cerebral circulation time improved from 8 to 6 seconds. Fifty-five minutes after the final SNP dose was delivered, the baseline diameter of the left M1 appeared to have been nearly restored and the PComA showed improved filling (Fig. 5, A and B). The circulation time on the right was also reduced (5.5 s). Large-caliber vessels on the right showed minimal dilation, but the distal A1 segment and distal

ACA in the interhemispheric fissure were better visualized. No important systemic hemodynamic changes were observed. Hypotension did not occur. ICP elevation to 21 mm Hg occurred transiently after the first dose and responded promptly to 3 cc of ventricular drainage. It did not occur subsequently, remaining at or below 17 mm Hg (Table 5). The neurophysiological parameters remained stable, and the procedures were terminated. The patient was returned to the neurosurgical intensive care unit, where TCD velocity measurements were noted to be dramatically improved (Table 4). The same evening, the patient demonstrated consistent purposeful movement of the previously plegic right side. Subsequent elevation of TCD velocities on the contralateral (right) side led to repeat cerebral angiography with angioplasty of the right supraclinoid carotid artery approximately 12 hours after the SNP treatment. Angiography was also performed on the left and demonstrated recurrent narrowing of the A1 and M1 segments that had been previously dilated by SNP. The cerebral circulation times were 5.5 and 6 seconds for right and left hemispheres, respectively. Endovascular maneuvers, using a smaller balloon catheter and a hydrophilic guidewire, permitted navigation of the patient's tortuous left ICA, and the M1 segment underwent angioplasty concurrently with the administration of additional SNP (12 mg) to enhance distal circulation in resistance vessels. Neither the supraclinoid carotid nor the A1 segment underwent angioplasty. The cerebral circulation times became 5 seconds bilaterally within 60 minutes of concurrent SNP treatment and angioplasty. Again, no hemodynamic or physiological changes were observed. MABP remained constant at 125 mm Hg. The next day, the patient was awake and alert with a GCS score of 10 (intubated), and he followed commands briskly with all extremities. Serum cyanate levels drawn on the evening after treatment were undetectable. CT of the brain performed 5 days after treatment demonstrated improvement in cerebral swelling. This patient was subsequently uneventfully discharged with no demonstrable neurological deficit (GCS score of 15).

Patient 3

A 38-year-old woman presented with aneurysmal SAH from a ruptured right carotid ophthalmic segment aneurysm. The clinical SAH grade (2) was III, and the radiographic SAH grade (1) was III (Fig. 6). The patient had no significant medical history but demon-

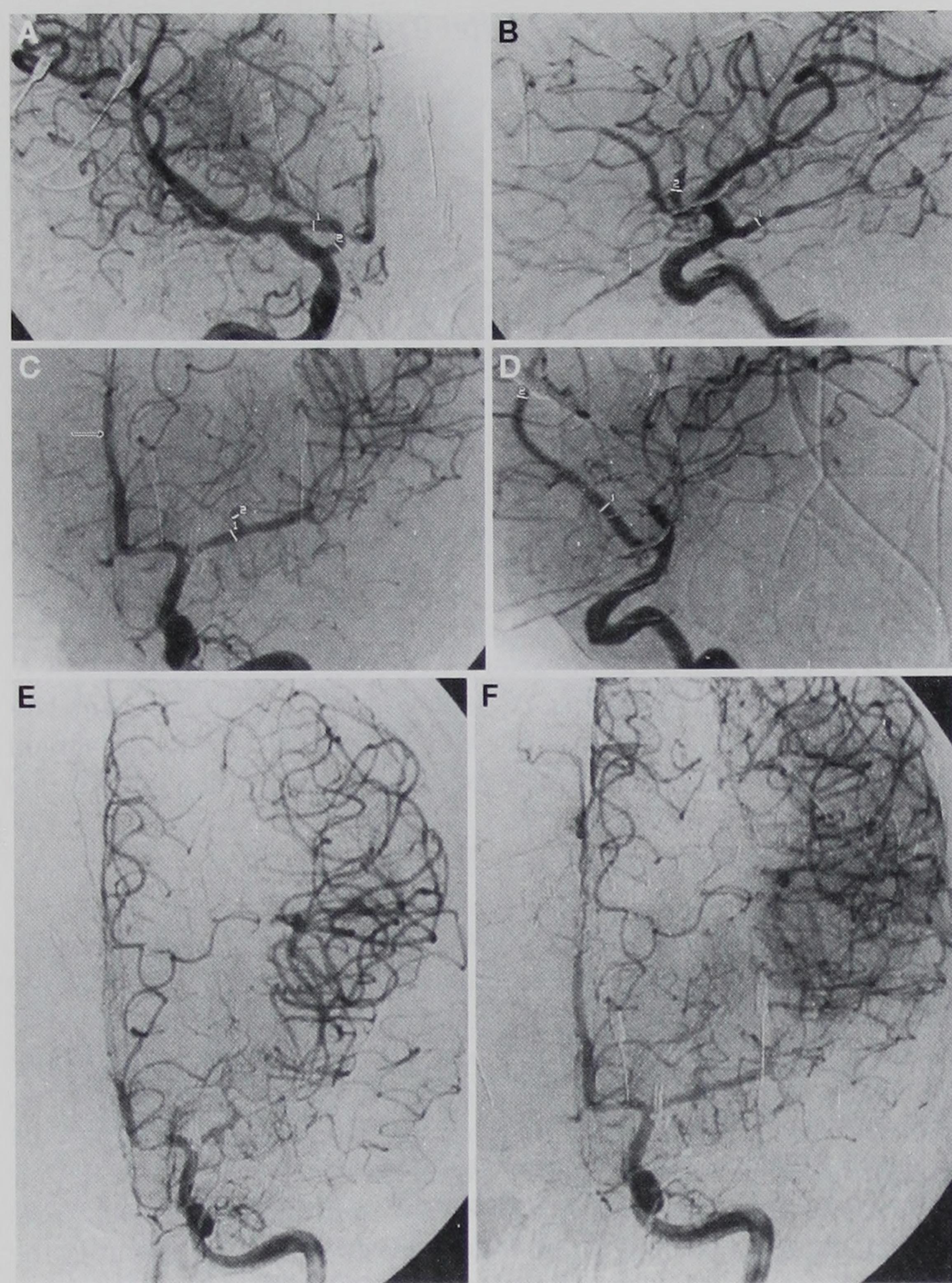


FIGURE 2. Patient 1. *A*, anteroposterior projection angiogram of the right cerebral ICA, obtained 24 hours after treatment. Persistent dilation of A1 (1) and PComA (2) can be observed. *B*, lateral projection angiogram of the right cerebral ICA, obtained 24 hours after treatment. Persistent dilation of PComA (1) with a focal region of recurrent vasoconstriction can be observed; A2 artery segment (2). *C*, anteroposterior projection angiogram of the left cerebral ICA, obtained 24 hours after treatment. Further dilation of the M1 (1) and M2 segments of the MCA (2) and A3 segment of the ACA (arrow) can be observed, compared with the same frame of the pretreatment angiogram (see *Fig. 1C*). *D*, lateral projection angiogram of the left cerebral ICA, obtained 24 hours after treatment. The dilation of the A3 segment of the ACA (2) can be seen; A2 artery segment (1). *E*, smaller anteroposterior projection angiogram (for comparison with *Panel F*) of the left cerebral ICA, obtained before treatment. The cerebral circulation time was 7.0 seconds. *F*, anteroposterior projection angiogram of the left cerebral ICA, obtained 24 hours after treatment. Note the enhanced distal circulation, compared with the same frame of the pretreatment angiogram (see *Panel E*). The cerebral circulation time was 5.0 seconds.

strated clinical evidence of significant cardiac dysfunction of unclear origin (ejection fraction, 35%). Coil embolization of the aneurysm was recommended and performed in an uncomplicated fashion on hospital Day 2 (SAH Day 4). Full-scale heparinization was instituted during

TABLE 3. Relative Diameters of Cerebral Vessels of Patient 1 before and after Treatment with Intraventricular Sodium Nitroprusside^a

	Pretreatment	Post-treatment (24 h)	% Baseline
RA1	0.96	1.93	201
RPCoMA	0.93	1.94	208
LA1	0.93	2.00 (estimated)	215
LM1	1.96	2.48	127
LM2	0.93	2.16 (estimated)	232
LA3	0.93 (estimated)	2.16	232

^a RA1, right A1 segment; RPCoMA, right posterior communicating artery; LA1, left A1 segment; LM1, left M1 segment; LM2, left M2 segment; LA3, left A3 segment. Relative diameters of cerebral vessels of Patient 1, measured digitally before and after treatment with intraventricular sodium nitroprusside, are shown. Absolute diameters, and therefore units of measurement, are omitted because calibration was not performed on the original angiograms.

the course of coil embolization and continued for 24 hours in routine fashion. Nimodipine, Decadron, and Dilantin were administered in routine fashion. The patient remained in the neurosurgical intensive care unit without complication. TCD velocity measurements (carotid index) were observed to increase on postoperative Day 2 (SAH Day 6) to 8.5 on the right and 9.2 on the left. No other clinical changes were observed. Intravascular volume expansion was performed in routine fashion using Swan-Ganz catheterization. On SAH Day 8, TCD values were noted to have once again increased (carotid indices, 8.5 and 9.3 on the right and left, respectively). There were no neurological symptoms. Cardiac performance was optimized, and pulmonary capillary wedge pressure was maintained at 14 mm Hg. Because of the patient's intrinsic cardiac dysfunction, however, the cardiac index did not surpass 3.25. On SAH Day 9, TCD values once again increased (carotid indices, 9.6 and 5.8 on the right and left, respectively) and Neosynephrine (American Regent Labs., Shirley, NY) and dopamine were added to the regimen. MABP was maintained between 110 and 120 mm Hg. On SAH Day 10, the patient experienced right hemiparesis and aphasia in the setting of a reduction of the MABP to 80 mm Hg, precipitated by bacteremia. The cerebral symptoms resolved promptly with restoration of the MABP to greater than 90 mm Hg. Antibiotic treatment was begun. On SAH Day 11, an aspiration pneumonia was diagnosed. In the evening, the patient again sustained a transient hemiparesis and aphasia in the setting of a transient decrease in the MABP. On SAH Day 12, TCD values remained markedly elevated (Table 6). The patient demonstrated no neurological symptoms. A temperature increase to 39°C occurred, and the antibiotic regimen was adjusted. Chest radiographs demonstrated pulmonary edema, and arterial oxygen saturation was marginal. Intubation was performed electively. Subsequently, the patient manifested right hemiplegia and aphasia. She was stuporous, with a GCS score of 7. The MABP was 110 mm Hg, and the cardiac index was 4.0. A frontal ventriculostomy was placed, and the patient was taken emergently for CT of the brain. The results of the CT were unremarkable, and the patient was taken directly to the angiography suite. Cerebral angiography disclosed severe vasoconstriction of the left M1, right M1, left and right supraclinoid carotid, and right A1 segments (Fig. 7, A-C). The cerebral circulation time of the left hemisphere was prolonged to 8 seconds and, of the right, to 7.5 seconds. The ICP was 10 mm Hg. Balloon angioplasty of the left M1 and both supraclinoid carotid segments was performed. Angioplasty of the right M1 and A1 could not be accomplished for technical reasons. SNP was administered via

TABLE 4. Mean Transcranial Doppler Velocities and Velocity Indices of the Cerebral Arteries of Patient 2 before and after Treatment with Intraventricular Sodium Nitroprusside^a

Vessel/Index	Hours after Treatment												
	-21	-1	5.5	19	26	46	49	69	75.5	91.5	97	116	122
RMCA	109	100	179	208	200	179	164	152	135	138	140	157	151
RACA	85	38	42	83	64	81	85	93	138	85	85	104	95
RICA	23	28	20	20	22	22	22	22	23	25	25	26	26
RCIX ^b	1.74	3.57	8.95	10.4	9.09	8.14	7.46	6.9	5.87	5.52	5.6	6.03	5.81
LMCA	211	252	81	145	145	150	152	151	169	169	133	126	123
LACA	69	40	85	164	151	169	121	110	169	152	100	145	181
LICA	25	20	23	34	33	33	33	33	33	33	27	29	28
LCIX ^b	8.44	12.60	3.52	4.26	4.39	4.55	4.61	4.58	5.12	5.12	4.93	4.34	4.39
AComA	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM

^a RMCA, right middle cerebral artery; RACA, right anterior cerebral artery; RICA, right internal carotid artery; RCIX, right carotid index; LMCA, left middle cerebral artery; LACA, left anterior cerebral artery; LICA, left internal carotid artery; LCIX, left carotid index; AComA, anterior communicating artery; NM, not measured. Mean transcranial Doppler velocities of the cerebral arteries of Patient 2, measured before and after treatment with intraventricular sodium nitroprusside (in cm/s), are shown.

^b Carotid index was calculated as follows: mean MCA velocity/mean cervical ICA velocity.

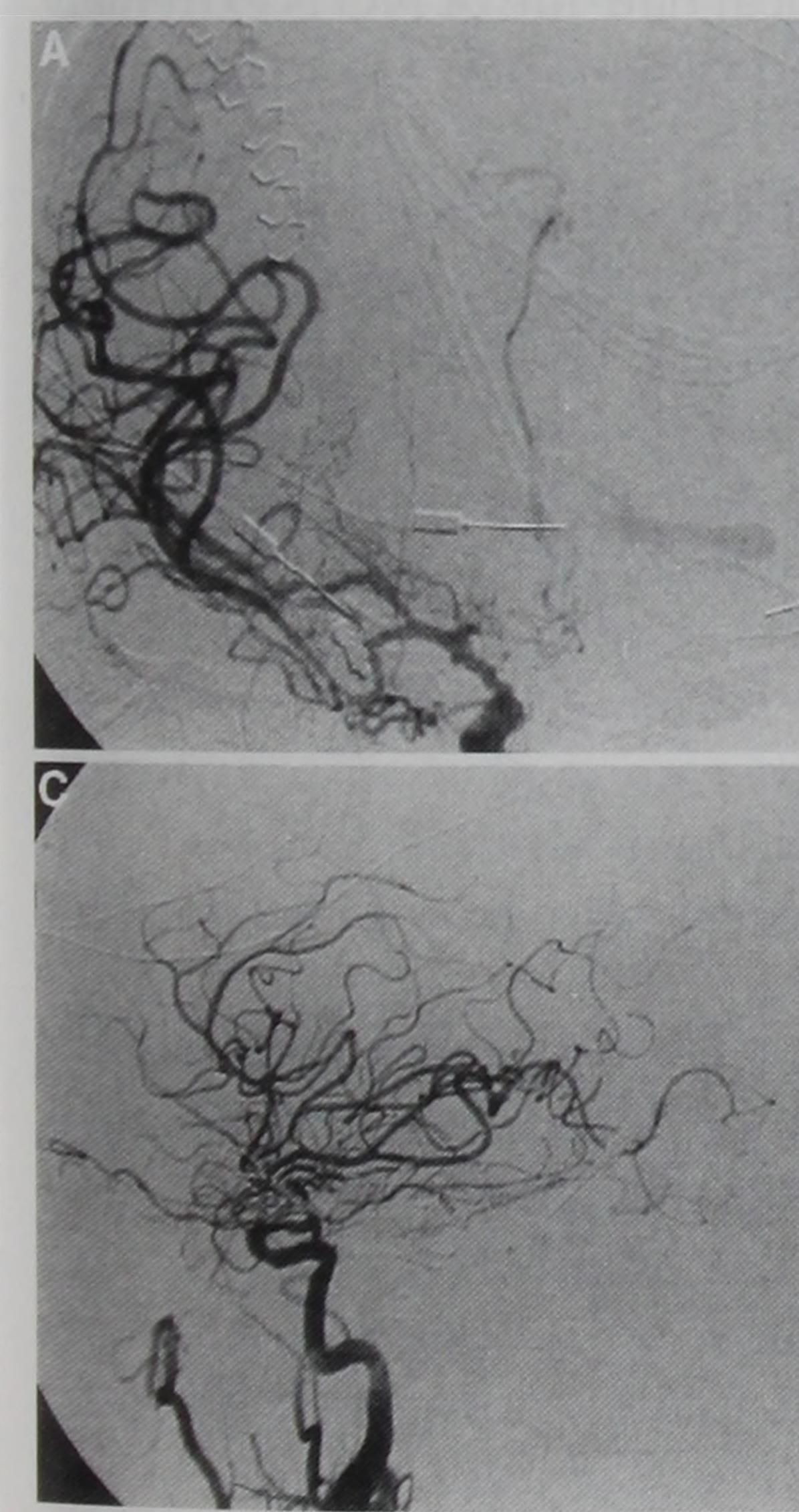


FIGURE 3. Patient 2.
A, anteroposterior projection angiogram of the right cerebral ICA, obtained before treatment with SNP. Note that the A1 segment is severely constricted. **B**, anteroposterior projection angiogram of the left cerebral ICA, obtained before treatment with SNP. Note that the A1 and M1 segments are severely constricted. The cerebral circulation time was prolonged (8.0 s, see text). **C**, lateral projection angiogram of the left cerebral ICA, obtained before treatment with SNP. The PComA is poorly visualized.

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the ventriculostomy in two doses to a total of 10 mg. The patient's blood pressure and ICP remained stable (Table 7). The left cerebral circulation time had improved to 6 seconds within 20 minutes of completion of SNP administration and angioplasty (Fig. 8, B and C). The right-sided cerebral circulation time had improved to 6.5 seconds after administration of SNP without angioplasty in the A1 or M1 segments and without appreciable change in the caliber of the larger conductance vessels on that side (Fig. 8A). The patient was returned to the neurosurgical intensive care unit, and pentobarbital coma was instituted to maintain an electroencephalographic burst suppression

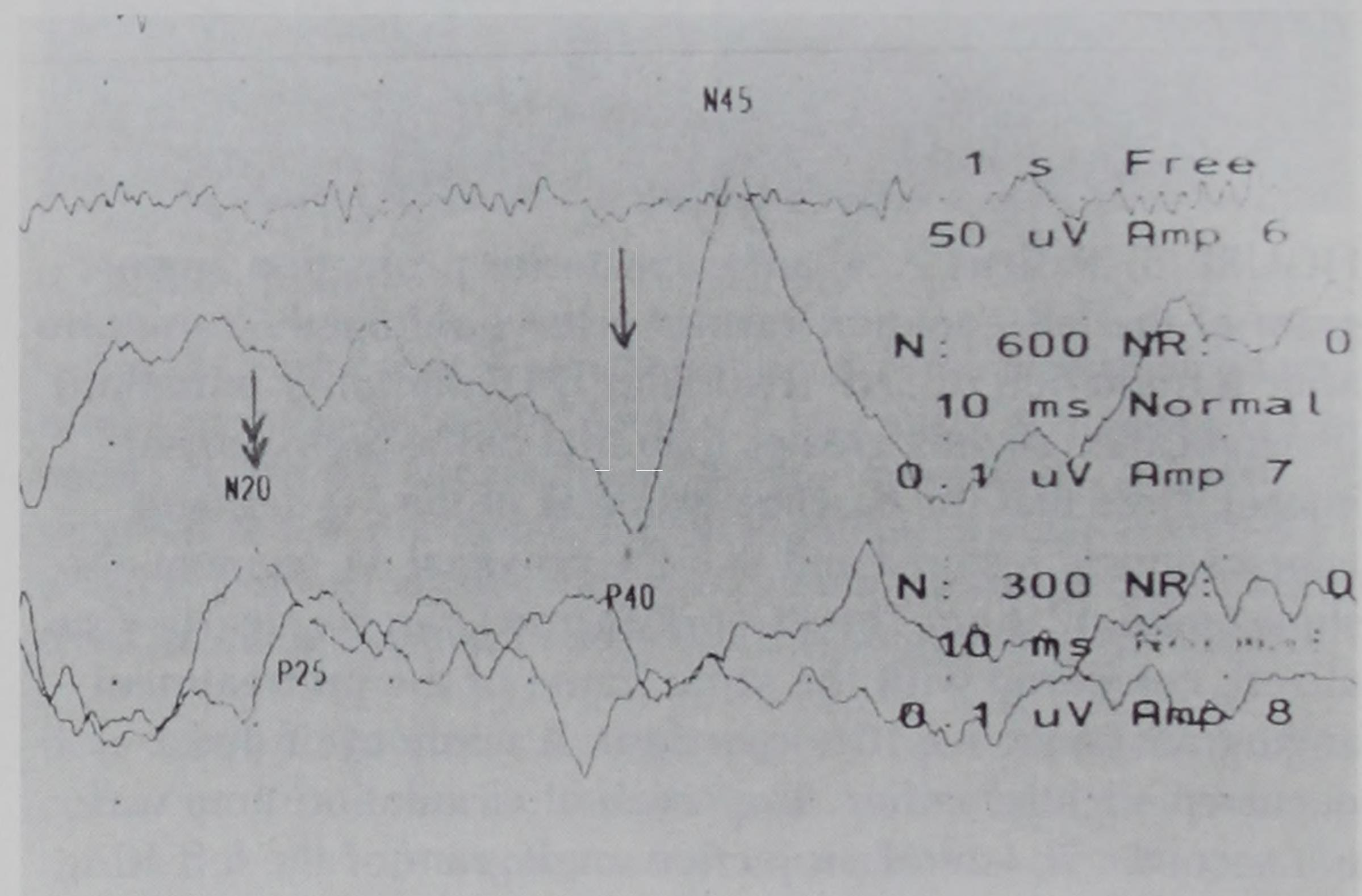


FIGURE 4. Patient 2. SSEPs from cortex of the left hemisphere (wave N20, representing the right upper extremity), demonstrating a leftward shift to 20.0 milliseconds (double arrow) from the baseline (lower trace, 23.9 ms) within minutes after administration of the first dose of SNP. The latency of the P40 wave representing the lower extremity was similarly decreased, from 51.5 to 47.7 milliseconds (comparison figure not shown).

pattern. TCD values measured 7 hours later demonstrated a dramatic reduction in velocities in the left MCA but no change in the right MCA and a slight increase in velocities in the right and left ACAs (Table 6). No intervention was added. TCD measurements 14 hours later demonstrated a substantial reduction in velocities of the vessels that had not undergone angioplasty (right MCA and ACA as well as left ACA) and a further reduction in left MCA velocity (Table 6). The low velocities persisted, and the patient was brought out of pentobarbital coma after 5 days. The patient demonstrated continual improvement without recurrence of symptomatic vasospasm and without a trace of neurological deficit (GCS score of 15). Volume expansion was maintained; pressors were gradually and uneventfully withdrawn. Cerebral angiography was not repeated. The ventriculostomy was discon-

TABLE 5. Measurements of Mean Arterial Blood Pressure and Intracranial Pressure of Patient 2 during Treatment with Intraventricular Sodium Nitroprusside^a

Time of dose (min)	0	20	26	36	41	46	53
MABP (mm Hg)	96	131	128	136	135	139	126
ICP (mm Hg)	21	15	16	16	16	16	17

^a MABP, mean arterial blood pressure; ICP, intracranial pressure. Measurements of MABP and ICP for Patient 2, obtained continuously during the first treatment (without angioplasty, see text) and recorded at times of administration of intraventricular sodium nitroprusside (4.0 mg/ml), are shown. Sodium nitroprusside was administered in 1.0- or 1.5-ml aliquots (see text). Entire treatment duration was 53 minutes.

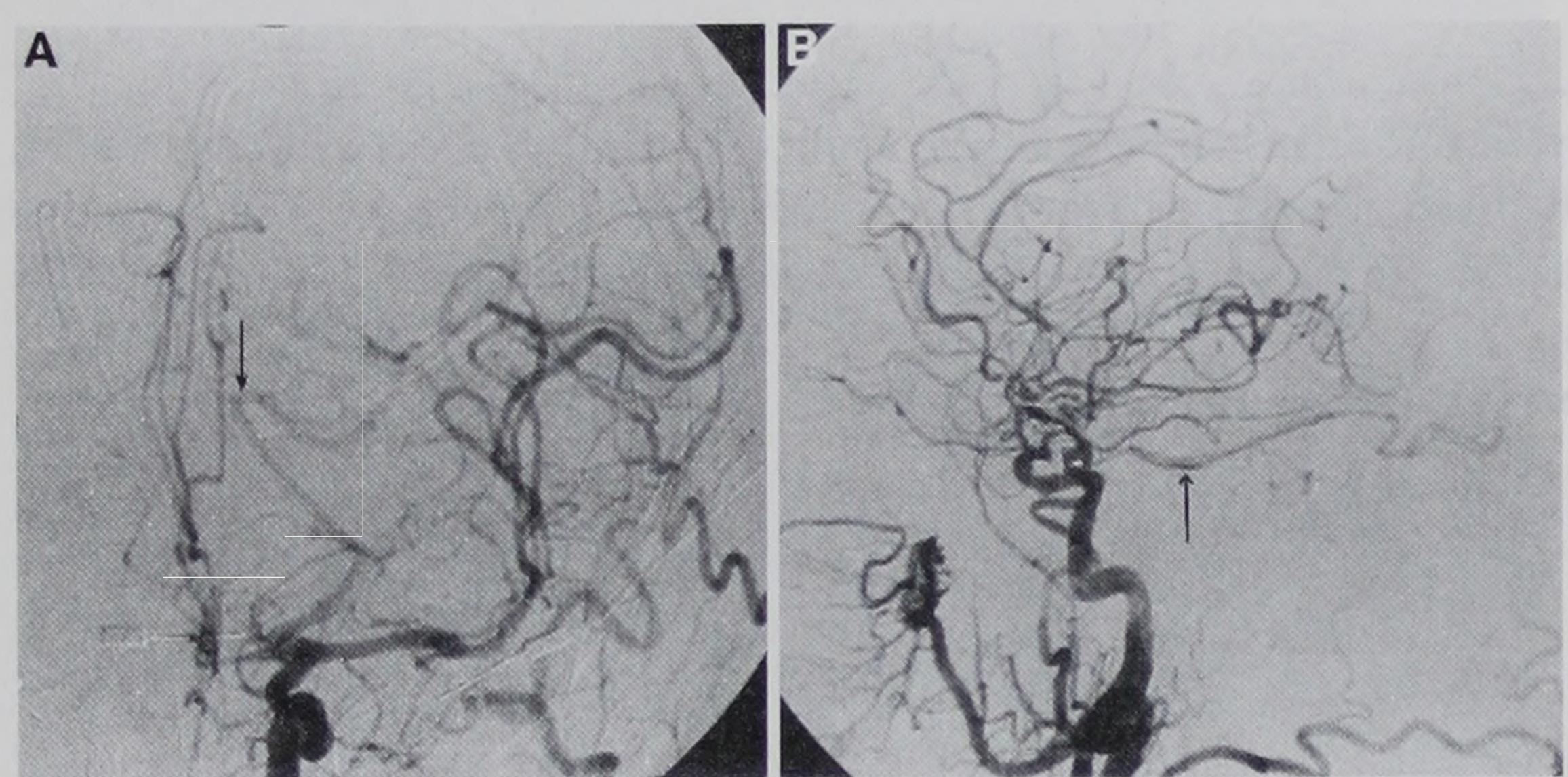


FIGURE 5. Patient 2. A, anteroposterior projection angiogram of the left common carotid artery, obtained 55 minutes after termination of SNP treatment (115 min after initiation) (magnification slightly greater than that of the pretreatment image). Note that the baseline diameter of the M1 segment appears nearly restored and that the proximal A1 segment also shows mild dilation. The PComA (arrow) can be clearly visualized, compared with the same frame of the pretreatment angiogram (selective ICA injection). A washout of dye occurred slightly earlier. The cerebral circulation time was 6.0 seconds. B, lateral projection angiogram of the left ICA, obtained 55 minutes after termination of SNP treatment (115 min after initiation). The PComA (arrow) can be clearly visualized, compared with the same frame of the pretreatment angiogram (see Fig. 3C).

tinued after a trial of clamping demonstrated no further ventriculomegaly. CT of the brain performed 10 days after treatment showed no residual abnormality. The patient was discharged on SAH Day 32 to a rehabilitation facility for a brief time for reconditioning purposes without neurological deficit. She then returned home, and her condition was excellent. She was independent at 7 months after treatment.

DISCUSSION

NO and cerebral vasoconstriction

NO is the smallest biologically active molecule known and is the mediator of an extraordinary range of physiological processes (6, 9). It is also a known physiological antagonist of endothelin 1, which is the most potent known mammalian vasoconstrictor (at least 10 times the vasoconstrictor potency of angiotensin II) (11), which has been implicated in CDCV by many investigations (3, 4, 7). NO donors have been demonstrated by direct observation to rapidly reverse induced cere-

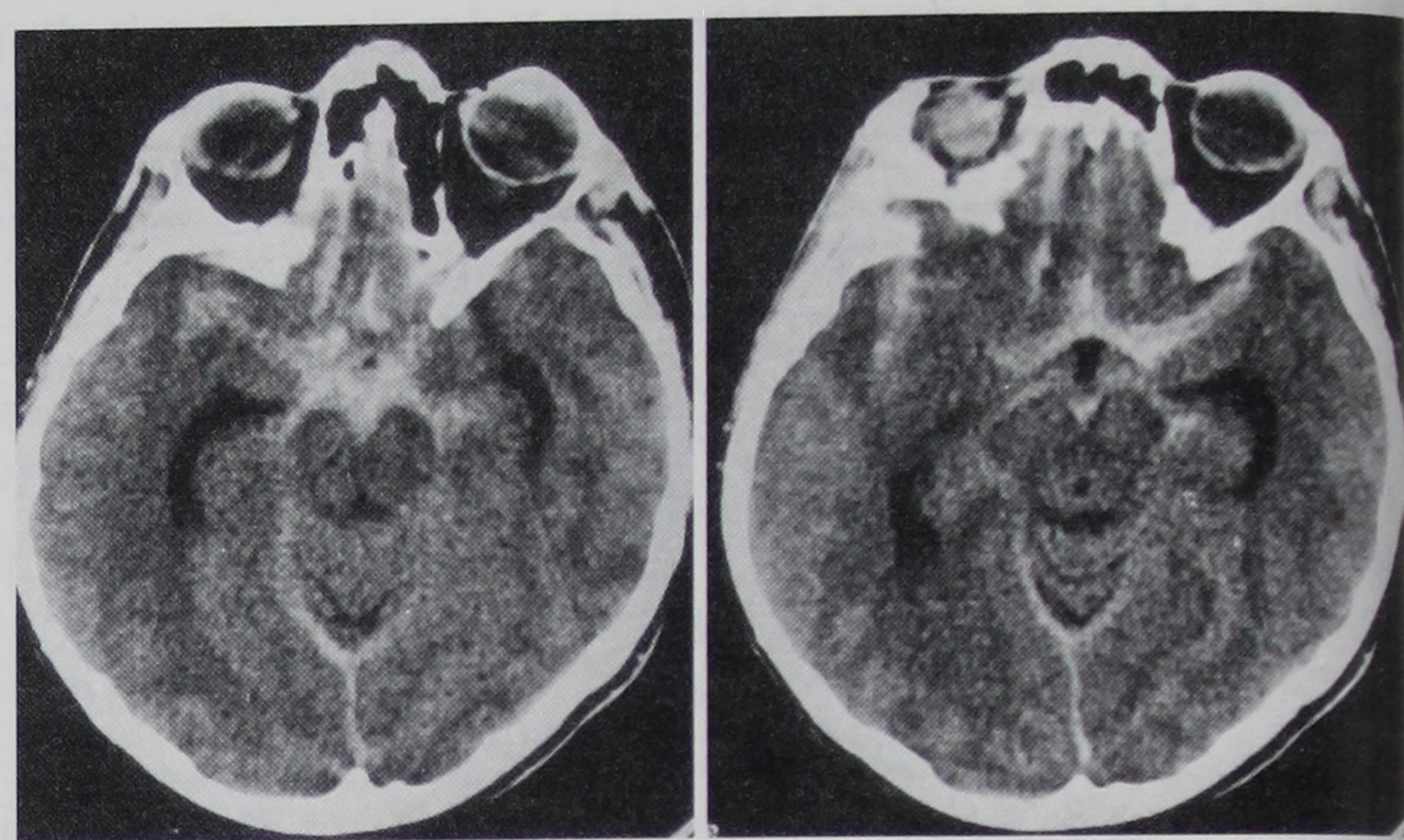


FIGURE 6. Patient 3. Different slices of unenhanced computed tomographic scans of the brain, obtained at admission, demonstrating diffuse SAH.

bral vasoconstriction in an animal model in which NO was delivered intrathecally to the adventitial side of the blood vessel (10). Systemic hypotension did not occur in this model, presumably because the biological half-life of NO is extremely short (5, 6), and the route of administration tended to favor local vasodilatory action.

These preliminary observations regarding three patients suggest that intrathecal delivery of NO donor compounds may be effective and durable in the treatment of severe refractory cerebral vasospasm that occurs after aneurysmal SAH in humans. Of three patients presenting in grave condition with profound neurological deficit, two have no residual deficit and one is greatly improved and living at home since relatively early (69 d) after the ischemic deterioration. Treatment of the latter patient, furthermore, was uncharacteristically delayed, because she had been hemiplegic from vasospasm for at least 12 hours before arriving at our hospital for further treatment.

The observed pattern of reversal of vasoconstriction by SNP and delayed segmental recurrence of the condition is consistent with a mechanism that depends on the presence and availability of a presumably finite substrate and that can apparently be at least temporarily overwhelmed. Although the durability of this treatment is not known, the effect obtained by the reported intraventricular doses seems to have been sufficiently lengthy to be useful under the dire circumstances of critical brain ischemia, the possibility of repeated treatments and increased dosage notwithstanding. Although a substantial vasodilation of large-caliber conductance vessels in response to SNP was demonstrated, the improvement in collateral circulation, dilation of smaller resistance vessels, and shortening of circulation time, sometimes without a dramatic change in the size of conductance vessels, seems to be an equally important effect of this treatment. Improved circulation time alone, at a constant cerebral perfusion pressure, may imply enhanced circulation at anatomic levels below angiographic resolution. NO is known to effect vasodilation through a cyclic guanosine monophosphate-mediated protein kinase activation mechanism (6, 9) that may be presumed to be functional at the level of the arteriole, because it is a muscularized vessel. The NO molecule derived from ITSNP,

TABLE 6. Mean Transcranial Doppler Velocities and Velocity Indices of the Cerebral Arteries of Patient 3 before and after Treatment with Intraventricular Sodium Nitroprusside^a

Vessel/Index	Hours after Treatment									Days after Treatment			
	-3	4	14.5	20.5	39	52	64.5	68	89	98	16	17	18
RMCA	303	312	136	136	113	140	132	176	167	186	82	85	93
RACA	214	224	64	162	112	31	212	200	52	47	159	100	107
RICA	35	20	44	33	25	31	26	29	33	50	47	47	45
RCIX ^b	8.65	15.6	3.09	4.12	4.52	4.52	5.08	6.07	5.06	3.72	1.74	1.81	2.07
LMCA	239	107	152	97	45	45	44	78	69	81	124	124	71
LACA	71	109	42	38	69	54	66	42	33	81	62	176	150
LICA	33	45	38	33	33	33	42	38	40	50	52	50	38
LCIX ^b	7.24	2.38	4.0	2.94	1.36	1.36	1.05	2.05	1.73	1.62	2.38	2.48	1.87
ACoA	NM	171	157	179	140	78	202	164	167	64	131	138	140

^a RMCA, right middle cerebral artery; RACA, right anterior cerebral artery; RICA, right internal carotid artery; RCIX, right carotid index; LMCA, left middle cerebral artery; LACA, left anterior cerebral artery; LICA, left internal carotid artery; LCIX, left carotid index; ACoA, anterior communicating artery; NM, not measured. Mean transcranial Doppler velocities of the cerebral arteries of Patient 3, measured before and after treatment with intraventricular sodium nitroprusside (in cm/s), are shown.

^b Carotid index was calculated as follows: mean MCA velocity/mean cervical ICA velocity.

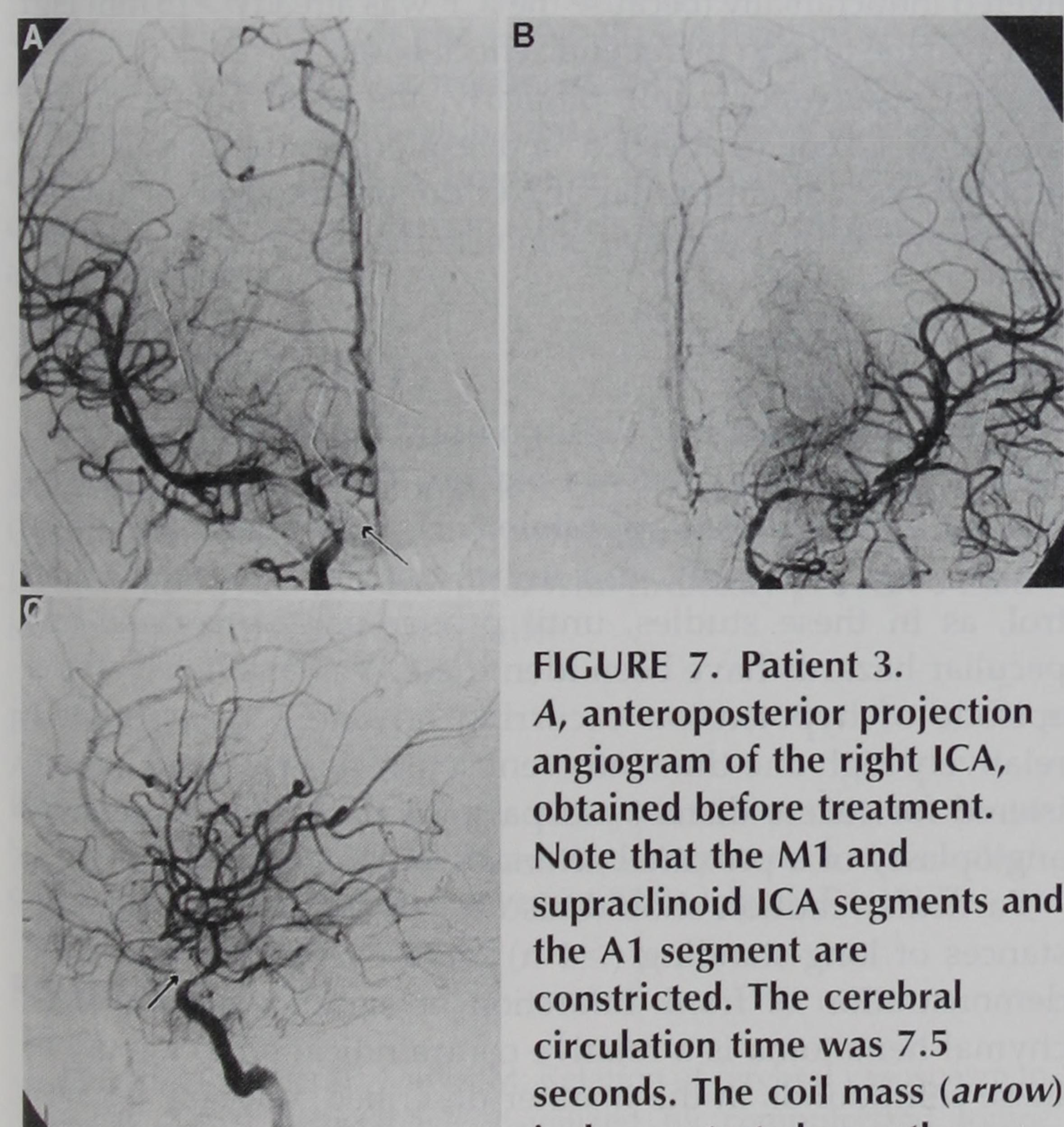


FIGURE 7. Patient 3. A, anteroposterior projection angiogram of the right ICA, obtained before treatment. Note that the M1 and supraclinoid ICA segments and the A1 segment are constricted. The cerebral circulation time was 7.5 seconds. The coil mass (arrow) is demonstrated over the supraclinoid carotid. B, anteroposterior projection angiogram of the left ICA, obtained before treatment. Note that the A1, M1, and supraclinoid ICA segments are constricted. There is reflux of contrast into the external carotid artery. The cerebral circulation time was 8.0 seconds. C, lateral projection angiogram of the left ICA, obtained before treatment. The subtracted coil mass (arrow) on the right is superimposed over the left ICA.

supraclinoid carotid. B, anteroposterior projection angiogram of the left ICA, obtained before treatment. Note that the A1, M1, and supraclinoid ICA segments are constricted. There is reflux of contrast into the external carotid artery. The cerebral circulation time was 8.0 seconds. C, lateral projection angiogram of the left ICA, obtained before treatment. The subtracted coil mass (arrow) on the right is superimposed over the left ICA.

having penetrated the adventitial side of the blood vessel, activates the soluble form of guanylate cyclase, which in turn converts guanosine 5'-triphosphate to cyclic guanylic acid. Through this latter second messenger, protein kinase activa-

TABLE 7. Measurements of Mean Arterial Blood Pressure and Intracranial Pressure of Patient 3^a

Time of dose (min)	0	10	20
MABP (mm Hg)	100	100	100
ICP (mm Hg)	10	9	11

^a MABP, mean arterial blood pressure; ICP, intracranial blood pressure. Measurements of MABP and ICP for Patient 2, obtained continuously during the first treatment (without angioplasty, see text) and recorded at times of administration of intraventricular sodium nitroprusside (1.0 mg/ml), are shown. Sodium nitroprusside was administered in 5.0-ml aliquots. Entire treatment duration was 20 minutes.

tion takes place and subsequently causes relaxation of muscular smooth muscle, resulting in vasodilation. Relatively thinner walls of smaller vessels could conceivably render them more readily susceptible to the effects of NO donors administered adventitiously, causing them to respond faster and improving cerebral circulation time. Such effects are consistent with the known physical properties of NO, which is a very small molecule capable of penetrating tissues directly. This is most evident in its interaction with blood vessels, which it may penetrate from the adventitial side (Mima et al. (4a), 1989, cited in Ref. 9), but would also be expected in brain tissue and blood clot. The computed tomographic scans of the patients in this study demonstrated substantial volumes of subarachnoid blood, which do not appear to have prevented the salutary penetration of ITSNP. It is also possible that ITSNP may penetrate the parenchyma by way of the ependyma of the ventricle, its effects in this way becoming, to a degree, independent of ventricular CSF circulation.

Considerations for route of administration

These salutary effects of vasodilation may be obtainable without precipitating intracranial hypertension or systemic hypotension. If these observations are confirmed, thought may be given to administering these compounds even more locally, by subarachnoid catheter or intraoperatively, under

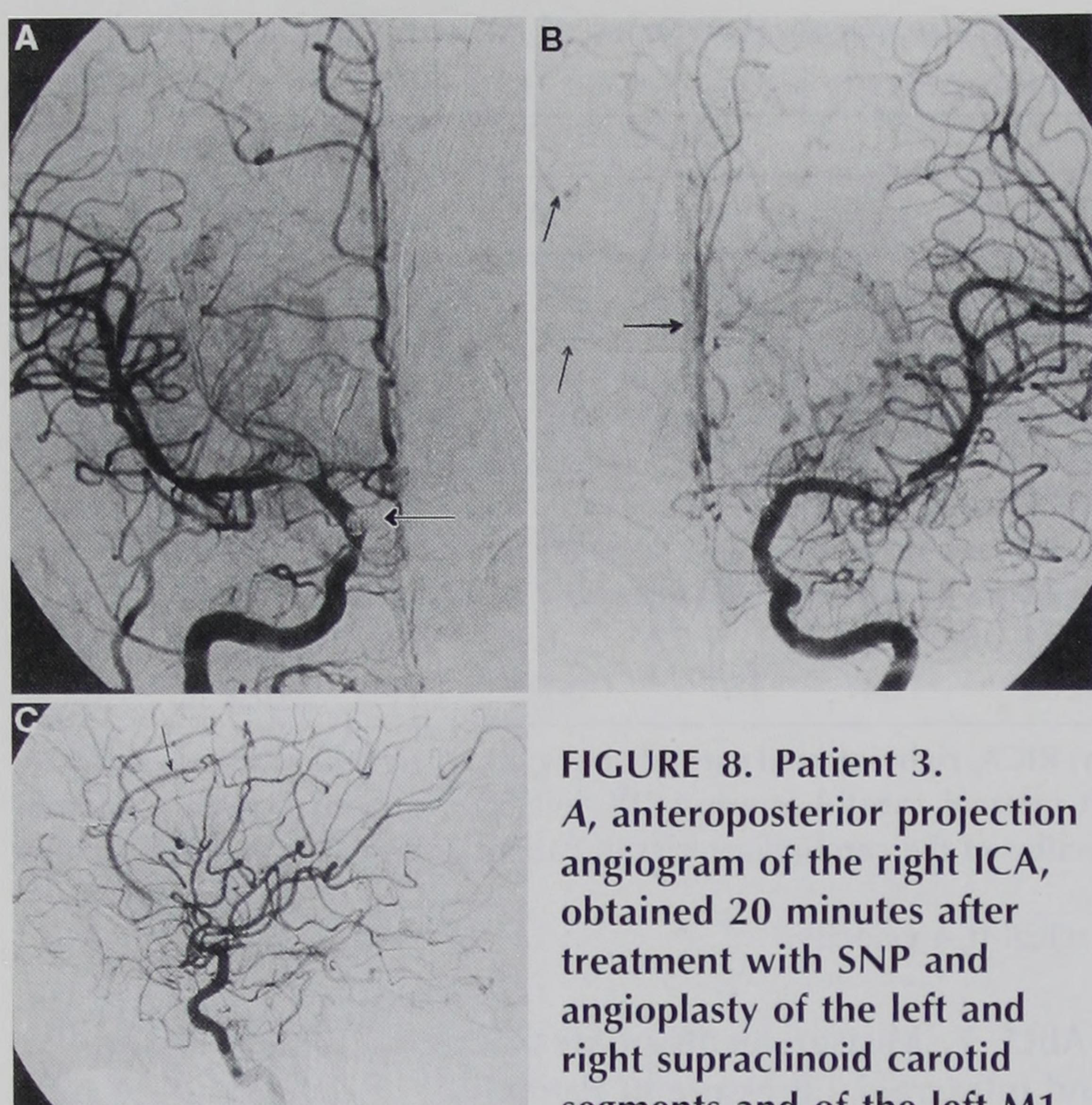


FIGURE 8. Patient 3.
A, anteroposterior projection angiogram of the right ICA, obtained 20 minutes after treatment with SNP and angioplasty of the left and right supraclinoid carotid segments and of the left M1 segment. Note that there is no appreciable change in the caliber of the larger conductance vessels (A1 and M1). The cerebral circulation time was 6.5 seconds. Filling of the ACA and lenticulostriate vessels was slightly better, compared with the same frame of the pretreatment angiogram (Fig. 7A). The subtracted coil mass (arrow) can be visualized over the supraclinoid carotid. B, anteroposterior projection angiogram of the left ICA, obtained 20 minutes after treatment with SNP and angioplasty of the left and right supraclinoid carotid segments and of the left M1 segment. Note that although the A1 segment shows no change in caliber, the distal ACA in the interhemispheric fissure and its branches (arrows) can be better visualized, compared with the same frame of the pretreatment angiogram (Fig. 7B). The cerebral circulation time was 6.0 seconds at constant MABP. C, lateral projection angiogram of the left ICA, obtained 20 minutes after treatment with SNP and angioplasty of the left and right supraclinoid carotid segments and of the left M1 segment. Improved filling of the ACA (arrow), which did not undergo angioplasty, is demonstrated in comparison with the same frame of the pretreatment angiogram (Fig. 7C).

the appropriate conditions of segmental vasospasm. We have observed a salutary clinical and angiographic effect of an NO donor administered locally in this manner. Targeted local therapy of this type would be a theoretical advantage where CSF pathways become compromised by brain swelling.

Timing and dosage

The timely delivery of this treatment for established CDCV also deserves emphasis. It is our practice to perform cerebral angiography and plan alternative therapy when medical treatment with HHH therapy has been maximized and ineffective for 1 hour. Although the clinical outcome for Patient 1

was relatively good, it might have been better had she been treated earlier.

It is emphasized that these observations regarding the use of intrathecal NO donors are preliminary and that optimal dosage and efficacy have not been determined. Whether higher doses can prevent recurrence of established CDCV is unknown. The structure of our dose escalation study imposed a limitation of 30 mg per procedure, and all patients received angioplasty either subsequently (Patients 1 and 2) or concurrently (Patient 3). Of note, two patients initially received ITSNP with obvious effect without angioplasty. Although we think that the vasodilatory effects of SNP and those of angioplasty are distinguishable in these cases (because of their separation in time and the distribution of the vessels affected), the definitive dosing, safety, and efficacy of these compounds must be rigorously demonstrated in clinical trials. In observance of this limitation of the present report, we deliberately avoided specific assertions regarding dosage. The concentration of medication delivered to Patient 2, for example, was increased in the interest of minimizing the fluid volume delivered intracranially (because the ICP was already >15 mm Hg) and also the time to therapeutic effect, based on previous experimental observations (10). Similarly, the ideal timing of this treatment is not established and exploring the possibility of prophylactic administration of NO donors to offset or prevent CDCV awaits the definitive demonstration of their safety.

Caution

The administration of these compounds in this manner is a serious undertaking that should not go unaccompanied by intense clinical, neurophysiological, and neuroanesthetic monitoring, preferably also under direct angiographic control, as in these studies, until proper parameters and any peculiar hazards have been identified. We have noted a brief episode of hypotension occurring on one occasion after a relatively high one-time intraventricular dose (12 mg) administered for severe distal vasospasm in the setting of cerebral angioplasty of a proximal arterial segment.

Particular caution should also be exercised under circumstances of long-standing (>4 h) brain ischemia, because the demonstration of frank infarction or significant intraparenchymal hematoma is a relative contraindication to the use of these compounds in the manner described, not only because of the risk of hemorrhagic conversion of infarction by reperfusion but also because of potential excitotoxic effects of NO. We have refrained from the use of these medications in the setting of medically refractory vasospasm with concurrent obvious infarction or intraparenchymal hematoma. Our current indications for including patients in this study are the same as those for cerebral angioplasty; patients with vasospasm refractory to HHH therapy as manifested by a failure to respond clinically within 60 minutes are eligible for treatment with or without cerebral angioplasty. If angiographic or neurophysiological improvement is not observed within 30 minutes of drug administration, patients are submitted to angioplasty where it is feasible (proximal conductance vessels not distal to M1 and A1 segments). We have observed neuro-

physiological improvement (shortened SSEP latencies) where the only discernible angiographic improvement seems to be in collateral circulation and improved circulation time, without a dramatic increase in the diameter of spastic relatively large conductance vessels. In these cases, we have combined cerebral angioplasty with intrathecal NO donor administration.

SUMMARY

In summary, this small preliminary experience with the intrathecal administration of NO donors for the treatment of cerebral vasospasm in humans seems to be favorable. Vasodilation may be effected without precipitating intracranial hypertension or systemic hypotension. Although this report emphasizes angiographic and ultrasonographic documentation of effect, an equally or more important effect of this treatment may be enhancement of cerebral blood flow at the level of the microcirculation. We have observed no adverse outcome in the extremely judicious, cautious, and vigilant use of this treatment. Further clinical studies are indicated, particularly using diffusion magnetic resonance imaging and xenon-enhanced CT for the sensitive evaluation of cerebral ischemia before and after treatment with ITSNP. Such studies will help to elucidate the potential use of ITSNP earlier in the course of CDCV, perhaps before an aggravated neurological deficit occurs. Dose escalation studies are currently underway at this institution.

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Reprint requests: Jeffrey E. Thomas, M.D., Division of Cerebrovascular Surgery and Interventional Neuroradiology, Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, PA 19107.

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COMMENTS

The authors present their interesting and exciting preliminary experience with intrathecal nitric oxide donors for the treatment of vasospasm from aneurysmal subarachnoid hemorrhage. They state the important caveats regarding the preliminary nature of their work and the possible negative effects of nitric oxide administration. Some questions remain regarding the ability of the treatment drug administered by this route to effectively reach all vessels in spasm or all territories at risk for ischemic injury. If the authors' goal was to increase cerebral blood flow, it seems some method of blood flow determination may be helpful in future studies to answer questions regarding dose and efficacy. Furthermore, the role of this treatment in relation to standard volume and cardiac manipulations, as well as other experimental techniques such as intrathecal thrombolytic therapy and intra-aortic balloon counterpulsation, will need to be more carefully assessed in further studies.

Warren R. Selman
Cleveland, Ohio

Thomas and Rosenwasser report three interesting cases in which intraventricular sodium nitroprusside (SNP) produced improvement in arteriographic caliber and transcranial Doppler velocity in patients with cerebral vasospasm. Intravenously (2) or intra-arterially (3) administered nitroprusside has been shown to be effective in a canine model of vasospasm, but clinical use has been limited by untoward systemic effects (4). Previous reports of efficacy for intrathecally administered SNP (ITSNP) in reversing vasospasm (1) suggested a potential benefit without concomitant hypotension, as observed in the three patients described in this report. Of note, the SNP effect seemed to be transient in some cases, similar to that seen with intra-arterially administered papaverine. In addition, in this report, patients did not immediately improve after the administration of SNP, although angioplasty produced rapid clinical improvement. The concurrent use of angioplasty in these patients complicates the analysis. Nevertheless, these