Early and aggressive treatment of medically intractable cerebral vasospasm with pentobarbital coma, cerebral angioplasty and ICP reduction

Rocco A. Armonda M.D., Jeffrey E. Thomas, M.D., and Robert H. Rosenwasser, M.D.

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

The authors present the unique experience of one neurovascular service under the direct supervision of the senior author, for which surgical, endovascular, and intensive care treatments were conducted in a select group of 32 patients with aneurysmal subarachnoid hemorrhage who had medically intractable symptomatic vasospasm.

A protocol of early and aggressive treatment was instituted using pentobarbital coma, cerebral angioplasty, and intracranial pressure (ICP) reduction. The patient population consisted of 25 women and seven men, whose ages ranged from 34 to 60 years (average 47 years). The patients' Hunt and Hess grades on presentation were as follows: Grade 0 (one); Grade I (three); Grade II (two); Grade III (nine); Grade IV (10); Grade V (seven). Microsurgical clipping alone was performed in 15 of 32 patients, endosaccular occlusion was performed in 17 of 20 patients, and two patients underwent combined treatment. Subsequent angioplasty was performed in 26 of 32 patients. Additionally, all 32 patients underwent treatment of increased ICP with ventriculostomy placement, removal of the bone flap (11), evacuation of associated intracranial hematoma (five), and decompressive obectomy (four).

Twenty-one patients survived and 11 died. Of the 21 survivors, seven have returned to work, live independently, and have no neurological deficits; eight require minimal assistance at home; four are in rehabilitation with moderate deficits at 3 months; and two remain in a persistent vegetative state.

In this group of aggressively treated patients who received pentobarbital cerebral protection, successful treatment of medically intractable cerebral vasospasm was related to time of treatment (< 2 hours), expeditious reduction of elevated ICP, and angioplasty.

Key Words * vasospasm * barbiturate therapy * angioplasty

Vasospasm caused by aneurysmal subarachnoid hemorrhage (SAH) remains a source of considerable morbidity and mortality that adversely affects between 10 and 20% of patients. The purpose of our study is to review the effects of using pentobarbital-induced coma on outcome in patients with medically intractable vasospasm.

CLINICAL MATERIAL AND METHODS

We report our experience in 32 patients with aneurysmal SAH who had medically intractable symptomatic vasospasm (Table 1).

TABLE 1
CHARACTERISTICS OF 30 PATIENTS UNDERGOING ANGIOPLASTY FOR TREATMENT OF VASOSPASM

Case No.	Age (yrs)	Grade	Aneurysm Location	Aneurysm Treatment	Deficits/TCD Measurements	Angioplasty/Pentobarbital	Associated Illnesses	Outcome
1	39	G0	bilat MCA	FT craniot, lt MCA clipping	receptive aphasia; rt hemiparesis	POD 1 HHH; POD 6 EDH evacuated, bone plate removed angioplasty X3 - 1 branch occlusion; PB begun at 2°	pneumonia, sepsis, septic arthritis, ALI, MOD	independent, mild rt paresis; walks w/ help
2	55	F3/GIII	lt PCoA ruptured ACoA	rt FT craniot, clipping, IVC	increased ICP, PH 4 lt hemiparesis; HHH TCD = 132–211, rt MCA	POD 3: PB > 2°, angioplasty, GDC of lt P CoA; bone plate removed	parotitis	lives at home; partially dependent for ADL
3	43	F3/GIII	ACoA	rt FT craniot ACoA clipping IVC	POD 10 lt hemiplegia	POD 11 angioplasty; POD 12 IVC; POD 12 PB after ICP increase > 20	pneumonia	independent, w/ mild lt hemiparesis
4	44	F3/GIII	lt PCoA	GDC	POD 4 UE drift; HHH; POD 5 temporal lobe/peduncle hem	POD 6 PB (6°), unresponsive to IVC; POD 7 bilat M ₁ angioplasty	pneumonia, sepsis ALI, MOD	lives at home; dependent for ADL
5	47	F3/GI	MCA, rt ACoA	rt craniot, clipping	POD 4 hemiparesis, responded to HHH, then increased	POD 4 angioplasty, POD 8 PB w/ elevated TCD; bone plate removed	ALI	independent; returned to work
6	49	F3/GIII	ACoA	rt FT craniot, clipping	swollen brain, intraop PB	immediate PB (<1°); bone plate kept off	pneumonia, ARDS; sepsis, w/ ALI MOD	independent, mild memory dysfunction; returned to work
7	60	GIV	PICA	GDC	IVC–VP shunt	PB (1°); angioplasty	pneumonia, ARDS; MOD	independent, returned to normal function
8	45	F3/GIII	PICA	GDC	IVC post-GDC; seizure IVC X3	PHD 2 PB (1°); intractable ICP vasospasm; diffuse small-vessel spasm	hypertension	died
9	55	F3/GIII	lt PCoA	IVC PHD 2 lt FT craniot PHD 3	POD 7 rapid obtundation, IVC for increased ICP; PHD 10 IVC X2	distal spasm, poor compliance	pneumonia, ALI MOD	died
10	38	F3/GIV	ACoA	rt FT craniot, intraop rupture; GDC of residual aneurysm	PHD 5 elevated TCDs	angioplasty of rt M ₁ carotid	pneumonia, tracheitis ALI	independent, returned to work
11	34	F3/GV	BA	IVC, GDC	PHD 7 increased ICP	PB; bifrontal craniot; angioplasty	pneumonia, line infection	dependent for ADLs, interacts minimally w/ family
12	42	GIV	ACoA	frontal craniot, clipping	elevated TCDs PHD 1, 3, 4	PB coma PHD 1; angioplasty PHD 3, 4, 5	pneumonia, line infection	works as a volunteer

13	44	GII	bilat ophth carotid	rt GDC	awoke hemiparetic; urokinase rt MCA, ACA, ICA	repeat angioplasty, extravasation of dye; PB begun	cardiac dysfunction, pneumonia	died
14	53	GII	ACoA	rt FT craniot	mild rt hemiparesis	angioplasty of lt ICA, MCA; PHD 4 increased hemiparesis PB begun	pneumonia, line infection	died PHD 7
15	40	F3/GIV	ACoA	GDC	IVC for hydrocephalus progressive ICP	decompressive craniot; PB	pneumonia	died
16	37	GI	rt ICA bifurcation	early vasospasm PHD 9, rt FT craniot	drowsy postop; elevated TCDs; frontal hematoma removed	elevated TCDs; PHD 31 VP shunt; PHD 32 angioplasty; PHD 33 PB; PHD 34 reop for frontal hematoma	hypotension & vasospasm during anesthesia for VP shunt	died
17	59	F3/GIV	distal ACA	rt frontal craniot, clipping	elevated TCDs; HHH; PHD 2 mild LE > UE paresis	PHD 4 severely elevated TCDs angioplasty PHD 5; obtunded rt ACA, supradinoid M ₁ ; PHD 7 angioplasty ICP 30–35, IVC; PHD 8 PB	intractable ICP	died PHD 9
18	42	F3/GIV	lt MCA	GDC of MCA; stuporous postop; 8 X 4-cm hematoma	PHD 3 PB begun	intractable ICP; PHD 6 increased hematoma; OR flap removed		died PHD 8
19	50	GV	ACoA	GDC, IVC X2	PB w/angiography did not awaken	angiography - extravasation of dye; progressive increase in ICP; IVC X2	intraventricular hemorrhage	died
20	38	F3/GIII	rt ophthalmic	GDC	rapid hemiplegia/aphasia; ratios lt 7.2/rt 8.7	angioplasty of bilat MCA, ICA, BP 1* after symptoms	pneumonia, rash arthralgia, cardiac dysfunction, ALI	independent
21	53	F4/GIII	ACoA	rt FT craniot, clipping	decrease in LOC; ratios rt 4.6/lt 1.6	angioplasty of rt MCA; PB 120 after decreased LOC	ARDS, cardiac dysfunction, sepsis, ALI, MOD	died of MI
22	42	F5/GV	lt giant supradinoid	GDC	hemiplegia; ratios rt 10.0/lt 13.0	unable to access; PB 1* after elevated TCDs	pneumonia; ARD, ALI	cared for by family; aphasia; rt hemiparesis
23	46	F3/GIII	lt ICA bifurcation	microsurgical clipping	hemiplegia; ratios lt 7.5/rt 4.1	angioplasty of lt MCA PB 360	pneumonia; line infection; ALI	monoparesis; lives w/ family
24	38	F4/GIV	lt MCA	microsurgical clipping; IVC	hemiparesis; ratios lt 8.1/rt 6.1	angioplasty bilat MCA; PB 1* after surgery (see case illustration)	pneumonia; lobar collapse, sepsis w/ line infection, ALI, MOD, pancreatitis pleural effusion, joint swelling (arthralgias)	mild monoparesis; lives w/ family
25	38	F3/GIII	ACoA	microsurgical clipping	aphasia, hemiplegia	PB after HHH for 1 hr; angioplasty of lt MCA	pneumonia-ALI SIRS/sepsis, MOD	independent, returned to work
26	33	F4/GV; GIV after IVC	basilar apex	GDC remodeling technique	PHD 6 increased TCDs PHD 9 SVO ₂ oligemia, TCD increased in VA/BA	PHD 6 anterior angioplasty, PHD 9 VA angioplasty/stent PHD 9 BA angioplasty	ARDS, MOD	independent returned to work
27	65	F4/GV; GIV after IVC	ACoA	GDC w/ bilat IVC	TCD increase, MAP increase	PB 2 hrs, bilat MCA angioplasty	ARDS, MOD	lives at home, minimal assistance
28	42	F4/GV GIV w/ IVC	lt MCA	GDC w/ IVC	increased ICP, temporal lobectomy, craniectomy	PB 1 hr, distal spasm, bilat MCA, ACA, PCA	ARDS, MOD, acute MI	lives at home, moderate disability, improving aphasia hemiparesis
29	46	F4/GV GIV w/ IVC	rt MCA	GDC w/ IVC	increased TCDs, ICP & MAP	bilat MCA angioplasty	SIRS w/sepsis MOD	independent, minimal assistance
30	47	F4/GIV	rt MCA ACoA	microsurgical	peak spasm on presentation	PB bilat MCA angioplasty	sepsis, pneumonia w/ ALI	moderate disability > 3 mos in inpatient rehab

* ACA = anterior cerebral artery; ACoA = anterior communicating artery; ADL = activities of daily living; ALI = acute lung injury; BA = basilar artery; craniot = craniotomy; EDH = epidural hematoma; FT = frontotemporal; hem = hemorrhage; IVC = intraventricular catheter placement; LE = lower extremities; MI = myocardial infarction; MOD = mature onset diabetes; PB = pentobarbital therapy; PCA = posterior cerebral artery; PCoA = posterior communicating artery; PHD = posthemorrhage day; PICA = posterior inferior cerebellar artery; POD = postoperative day; SCA = superior cerebellar artery; SIRS = systemic inflammatory response syndrome; UE = upper extremities; VP = ventriculoperitoneal.

† Grades are based on the systems of Hunt and Hess (G) and Fisher (F)

All patients underwent an initial evaluation, including review of outside angiographic or computerized tomography (CT) studies when not performed at our institution. These 32 patients in whom high-dose pentobarbital administration was part of combined therapy for the treatment of medically intractable vasospasm are a subpopulation of 528 patients with aneurysms treated by the senior author (R.H.R.) in a 3-year period from July 1995 to 1998. All patients received conventional hypervolemic, hypertensive, hemodilution (HHH) therapy, with early use of pentobarbital combined with angioplasty and other measures to decrease intracranial pressure (ICP). If patients were rated Hunt and Hess Grade III or above and had hydrocephalus, they first underwent intubation and then placement of a ventriculostomy, arterial line, and a central line for subsequent Swan-Ganz catheterization (Fig. 1). Following diagnostic angiography, the senior author determined whether to proceed with endovascular coiling or with open microsurgical treatment. Endovascular coiling was reserved primarily for the treatment of patients with posterior circulation aneurysms, poor-grade patients, or elderly patients considered medically poor candidates for surgery. Other criteria for treatment included adequate vascular access for the guiding and microcatheters as well as the configuration of the

aneurysm neck and associated branches of the parent artery. All patients underwent neuromonitoring and were transported to the neurosurgical intensive care unit where HHH therapy was instituted, and they were monitored for vasospasm and provided with medical support. The patient population consisted of 25 women and seven men, with ages ranging from 34 to 60 years (average 47 years). Modified Hunt and Hess grades at presentation were as follows: Grade 0, one patient; Grade I, three patients; Grade II, two patients; Grade III, nine patients; Grade IV, 10 patients; Grade V, seven patients. Sole treatment with microsurgical clipping was performed in 15 of 32 patients; endosaccular occlusion was performed in 17 of 20 patients; and two patients underwent combined treatment. Coil placement was used in endosaccular aneurysms in poor-grade patients (four anterior communicating artery, one bilateral carotid-ophthalmic, one carotid-ophthalmic, one posterior communicating artery, five middle cerebral artery [MCA], and one giant supraclinoid carotid), for posterior circulation aneurysms (two basilar artery, two posterior inferior cerebellar artery aneurysms), or in patients with multiple medical illnesses who were unlikely to survive surgical intervention. Patients underwent transcranial Doppler (TCD) ultrasound twice daily. Cardiac output was maximized according to individual starting curves determined by Swan-Ganz catheter measurements. Early pentobarbital therapy was instituted within 2 hours in patients whose neurological deficits persisted despite HHH therapy. A loading dose of 2 to 5 mg/kg was used with continuous electroencephalographic monitoring to maintain burst suppression with between four and six cortical spikes per minute (Table 2). Patients received fluids and pressors preoperatively, if necessary, to avoid hypotension. Subsequent angioplasty was performed in 26 of 32 patients. Additionally, all 32 patients underwent treatment for increased ICP with ventriculostomy placement, removal of the bone flap (11 patients), evacuation of associated intracranial hematoma (five patients), or decompressive lobectomy (four patients).

TABLE 2	
PROTOCOL FOR PENTOBARBITAL THERAPY ADMINISTRATION	
1)	5–10 mg/kg load
2)	preload w/fluid to avoid hypotension
3)	EE G monitoring w/ 4–6 spikes prior to confirming burst suppression
4)	aggressive pulmonary toilet
	a. chest physiotherapy
	b. nebulizer treatment
	c. suctioning
	d. early bronchoscopy for pneumonia/lober collapse
	e. prolong use 5–7 days perform tracheostomy
5)	aggressive ID vigilance
	a. daily CSF surveillance (cell count/differential/culture/Gram stain/protein/glucose)
	b. observe CBC for bacteremia
	c. low-grade hypothermia/hyperthermia
	d. hyperglycemia
	e. rigorous line asepsis/changing of line & sites with fever or infection of a site
6)	nutritional support
	a. early parenteral nutrition
	b. once active peristalsis enteral feeds
	c. early percutaneous jejunostomy if >7–10 days expected
* CBC = complete blood count; CSF = cerebrospinal fluid; EE G = electroencephalogram; ID = infectious disease.	

ILLUSTRATIVE CASES

Case 20

This 38-year-old woman with Hunt and Hess Grade III and Fisher Grade 3 aneurysmal SAH underwent Guglielmi detachable coil (GDC) treatment of her right ophthalmic artery aneurysm (Fig. 1 upper left and right).

Fig. 1. Case 20. Imaging studies. Upper Left: Digital subtraction right ICA angiogram with right orbital oblique view demonstrating a carotid-ophthalmic artery aneurysm. Measurements of aneurysm used to select initial coils. Upper Right: Angiogram obtained after initial endovascular treatment (postendovascular occlusion of aneurysm) with an activated clotting time (250 seconds) twice baseline. Lower Left: Initial CT scan demonstrating Fisher Grade 3 SAH with dilation of temporal horns. Lower Right: Angiogram demonstrating severe vasospasm of left supraclinoid carotid, M₁ segment, and A₁ segment now with medically intractable vasospasm with clinical aphasia and hemiplegia.

She received HHH therapy because of evidence of elevated blood flow velocity detected on TCD ultrasonography posthemorrhage (PH) Day 3 (mean blood flow velocity in the right MCA increased from 96 to 161 to 224 cm/second and in the left MCA it increased from 102 to 155 to 220 on PH Day 5.) Clinically, she remained asymptomatic until PH Day 7; at which time she became diaphoretic, aphasic, and had loss of antigravity strength in the right upper extremity. The TCD ratios measured in the right MCA were 7.2 to 8.5 to 9.1 and the right MCA mean blood flow velocities were 255 cm/second; in the left MCA, TCD ratios were 3.9 to 9.3 to 8.0 and left MCA mean velocities were 207 cm/second. Her clinical status improved after receiving aggressive HHH therapy. On PH Day 9 the patient experienced a repeated episode of hemiplegia and aphasia; her mean arterial pressure was 107 to 111 mm Hg and she was treated with 250 ml³ of 5% albumin. Strength increased to 4/5 in the right upper extremity and 3/5 in the left lower extremity. Several hours later her right side worsened to hemiplegia and aphasia. Pentobarbital was administered and emergency CT scanning was performed. Ventriculostomy and cerebral angiography were performed, which demonstrated severe bilateral vasospasm of the internal carotid arteries, and MCAs, more on the left than right. Angioplasty was performed in the left M₁ segment, supraclinoid carotid, and right supraclinoid carotid arteries (Figs. 1 lower left and right and 2 upper left).

Fig. 2. Case 20. Upper Left: Controlled angiogram immediately after balloon dilation of left M₁ segment and left supraclinoid carotid. Upper Right: Angiogram demonstrating persistent vasospasm of right MCA. Lower Left: Digital subtraction angiogram in which the roadmapping technique is used showing microballoon dilated in the right M₁ segment. Lower Right: Controlled angiogram of right ICA immediately after angioplasty.

Postprocedure, the patient remained in a pentobarbital-induced coma for 3 days, which was progressively decreased by 25% each postprocedure day. Transcranial Doppler ultrasonography was performed postprocedure. On postoperative Day 1, TCD ratios were: left MCA 2.3 (mean MCA velocity 88 cm/second) and right MCA 3.1 (mean MCA velocity 136 cm/second). Over the following 7 days the right-sided TCD ratios progressively increased. The patient did not tolerate HHH therapy, with decreased cardiac contractility (cardiac ejection fraction 57-35%). On PH Day 23, repeated angiography was performed because the patient was not tolerating HHH therapy and had persistent right MCA ratios of between 5 and 7. Angioplasty was performed in the stenotic right M₁ segment (Fig. 2 upper right and lower left and right). Comorbidity features included acute lung injury with pneumonia, pulmonary edema, decreased cardiac contractility, and inflammatory arthritis of the right foot/ankle/toe. The patient's cardiac dysfunction resolved after discontinuation of HHH therapy. She was progressively weaned, extubated, and discharged home for outpatient rehabilitation. Currently, the patient lives at home and has returned to work at her 3-month follow up.

Case 24

This 38-year-old woman presented with Hunt and Hess Grade IV SAH from a ruptured left MCA aneurysm, as well as with sylvian fissure hematoma and hydrocephalus (Fig. 3 A-B).

Fig. 3. Case 24. A: Computerized tomography scan at presentation demonstrating Fisher Grade 4 SAH and sylvian fissure hematoma. B: Preoperative angiogram from an outside institution demonstrating a right MCA aneurysm. C: Intraoperative angiogram demonstrating obliteration of the aneurysm and normal filling of superior and inferior trunks. D: Postoperative x-ray film of the chest, during a period of severe respiratory distress, demonstrating alveolar consolidation in four lung quadrants. E: Subsequent x-ray film of the chest demonstrating evidence of marked improvement after tracheostomy and bronchoscopy. F: Angiogram revealing severe cerebral vasospasm that is affecting the right supraclinoid carotid artery and right M₁ segment. G: Angiogram demonstrating balloon angioplasty of the right supraclinoid carotid artery and M₁ segment. H: Control angiogram immediately after balloon angioplasty demonstrating increased lumen diameter.

On admission, she underwent intubation, was experiencing contralateral hemiparesis, and also underwent a ventriculostomy. A left frontotemporal craniotomy and microsurgical clipping of the left MCA aneurysm were performed. Intraoperative angiography confirmed aneurysm clipping and normal filling of the superior and inferior trunks (Fig. 3C). Due to significant cerebral edema, pentobarbital therapy was initiated; the bone flap was left out and the dura left open. The patient remained in a pentobarbital-induced coma and ICP was controlled using ventricular drainage. On postoperative Day 3, she developed hypoxia and required increased positive end-expiratory pressure, fraction of inspired oxygen, and aggressive pulmonary toilet. There was evidence of early pancreatitis with pleural effusion and hypoxia on postoperative Day 4, and the patient was continued on bowel rest with hyperalimentation via total parenteral nutrition. On postoperative Day 6 she developed increased ICP to 22 mm Hg and increased cerebrospinal fluid output. Computerized tomography scanning revealed no new hemorrhage or ventriculomegaly. Transcranial Doppler ultrasonography demonstrated increased right-sided velocities from means of 130 to 160 cm/second with ratios increased from 2.0 to 5.0 on the right. Her pulmonary insufficiency was worsening, and an x-ray film of the chest demonstrated lobar collapse with pneumonia (Fig. 3D). Subsequently, she underwent emergency bronchoscopy and tracheostomy (Fig. 3E). On PH Day 10, while receiving pentobarbital therapy, she had significantly elevated blood flow ratios, which increased from 3.9 to 7.9 on the right and from 3.2 to 4.1 on the left; mean right MCA velocities increased from 138 to 205 cm/second and then to 220 cm/second. Angiography was performed, which revealed evidence of vasospasm of the bilateral M₁ segment (Fig. 3F). She underwent angioplasty (Fig. 3 F-G); postangioplasty her TCD measurements showed a reduced mean right MCA velocity of 143 cm/second and a left MCA velocity of 112 cm/second; a mean right MCA ratio of 4.9 and left MCA ratio of 2.0. Pentobarbital therapy was progressively decreased over the next 5 days, with improved pulmonary toilet, aggressive chest physiotherapy and nebulizers. Subsequently, she was discharged to inpatient rehabilitation.

Progressive improvement was noted at 6-week and 12-week follow-up examination. Currently, she is doing well at 10 months postoperatively and her autologous bone flap was replaced. She has no focal neurological deficits and has returned to a regular work schedule.

Case 22

The patient was a 42-year-old male jockey, who suffered SAH while riding his horse. He fell to the ground and experienced a seizure, respiratory arrest, and had a likely aspiration. He was resuscitated and remained unresponsive in a coma at initial assessment (Hunt and Hess Grade V). Computerized tomography scanning of the head demonstrated evidence of diffuse SAH, hydrocephalus, and a 3.5-cm mass revealed as the giant aneurysm (Fig. 4A).

Fig. 4. Case 23. Imaging studies. A: Computerized tomography scan at presentation demonstrating Fisher Grade 4 SAH with a globoid hematoma representing a giant supraclinoid aneurysm. B: Left digital subtraction angiogram demonstrating giant supraclinoid aneurysm (unable to discern a discrete neck in this view). C: Early-phase angiogram, demonstrating a jet of contrast material, which suggests a narrow aneurysm neck. D: Deployment of initial coils, stable position achieved without displacement into the ICA, M₁, or A₁ segments. E: Control angiogram demonstrating obliteration of aneurysm and filling of A₁ and M₁ segments and their respective branches.

Angiography confirmed a giant left supraclinoid artery aneurysm (Fig. 4B). Ventriculostomy was placed, and his neurological status improved to a Hunt and Hess Grade IV. Due to pulmonary aspiration, he developed pneumonia and subsequently adult respiratory distress syndrome (ARDS), requiring pressure-controlled ventilation. On PH Day 4, he had a significant increase in his TCD measurement, increased CSF drainage via his ventriculostomy and elevated ICP to 20 mm Hg. The TCD values increased from PH Day 3 to PH Day 5 (right MCA mean velocities of 83 to 151 to 183 to 227 to 255 cm/second and left MCA mean velocities 133 to 200 cm/second); over the same period TCD ratios increased (right 3.3-10.3; left 5.2-13.3). Repeated angiography confirmed severe bilateral vasospasm of both M₁ vessels and the supraclinoid carotid artery, as well as of the bilateral A₁ segments. Because of the presence of an untreated ruptured giant aneurysm, he was not a candidate for angioplasty or papaverine therapy. He was placed in pentobarbital-induced coma and aggressively treated for his aspiration pneumonia and ARDS. Tracheostomy and bronchoscopy were performed to improve oxygenation and pulmonary toilet. Moderate HHH therapy was continued as tolerated. On PH Day 8, endovascular exploration of the aneurysm was performed, which demonstrated a small-neck aneurysm that made GDC treatment of the aneurysm possible (Fig. 4C-E). Attempts to perform angioplasty in the left M₁ segment were thwarted by the mass effect from the giant aneurysm fundus. The patient was progressively weaned from his pressure-support

ventilation, and pentobarbital therapy was decreased over a 4-day period without increase in his ICP. Currently, the patient lives at home, interacting with his family and requiring only partial assistance with activities of daily living. He is nonambulatory but beginning to stand and has moderate aphasia.

Case 26

This 33-year-old man presented with a Hunt and Hess Grade V SAH resulting from rupture of a basilar bifurcation aneurysm (Fig. 5A-B).

Fig. 5. Case 25. Imaging studies. A: A CT scan demonstrating diffuse SAH with interpeduncular hematoma and hydrocephalus and rehemorrhage in the cerebral peduncle before treatment. B: Angiogram demonstrating evidence of complex basilar bifurcation aneurysm with bilobed configuration. C and D: Angiograms obtained prior to coil placement. Anteroposterior (C) and lateral (D) views, demonstrating obliteration of aneurysm and normal filling of the PCAs (accomplished using balloon remodeling techniques). E: Posthemorrhage Day 8 angiogram demonstrating dissection of the right vertebral artery and posterior circulation spasm. F and G: Control angiograms after angioplasty and stenting of dissection (F), and after undergoing basilar artery angioplasty (G) for associated vasospasm.

The patient improved to Grade IV following placement of a ventriculostomy. Because of increased ICP, a CT scan was obtained, which demonstrated evidence of new hemorrhage into the cerebral peduncle. The patient had progressive pulmonary distress with oxygen desaturation and underwent emergency bronchoscopy for lobar collapse. Posthemorrhage Day 3, he underwent GDC treatment of the aneurysm, with balloon remodeling techniques (Fig. 5C-D). Elevated TCD values were noted on PH Day 3. He underwent balloon angioplasty of the anterior circulation and was placed in pentobarbital-induced coma. Posthemorrhage Day 8, he had SjVO₂ changes that demonstrated increased oxygen extraction consistent with an oligemic state. Posterior circulation TCD values were elevated; a repeated CT scan was obtained that revealed bilateral hypodensities of the PCAs. A cerebral angiogram demonstrated an occluded right vertebral artery (Fig. 5E). Emergency vertebral artery angioplasty with stent placement was performed, followed by basilar artery angioplasty (Fig. 5F-G). His course was complicated by pneumonia, sepsis, pancreatitis, and prolonged intubation. He underwent placement of a ventriculoperitoneal shunt and, following a prolonged intensive care unit course, he was transferred to rehabilitation. At 3-month follow-up review he had recovered substantially; he was living independently and was cutting his lawn and cleaning the family swimming pool.

RESULTS

Twenty-one patients survived and 11 died after undergoing treatment using this protocol (Table 1); associated morbidity factors included pneumonia with acute lung injury (18 patients) and fulminant ARDS (six patients), sepsis (16 patients), pancreatitis (five patients), cardiac dysfunction (three patients), and septic arthritis and pulmonary embolus (one patient each). Infectious complications were monitored by closely following the differential white-cell count, early use of tracheostomy and aggressive pulmonary toilet (Case 24). Of the 21 survivors, seven have returned to work, live independently, and have no neurological deficits; eight require mild assistance at home; four are in rehabilitation and have moderate deficits at 3 months; and two remain in a vegetative state. Factors associated with a poor outcome include a delay of more than 2 hours in recognition or intervention for vasospasm (Cases 8, 9, and 16; Table 1), associated morbidity factors related to preexisting medical condition combined with pentobarbital therapy (Case 21), branch occlusion with vessel rupture (Case 13), and intractable ICP related to small-vessel vasospasm (Cases 14 and 15). In a selected group of poor-grade patients, a single cause could not be identified and was likely related to the patient's poor clinical grade (Cases 18 and 19).

DISCUSSION

The common goal in treating vasospasm in patients with symptomatic SAH involves minimizing the neuronal injury. Approaches are directed toward two major avenues, including improving cerebral blood flow (CBF) as well as reducing cellular energy demands, thereby avoiding a demand/supply mismatch that results in irreversible neuronal injury.[2] Improving CBF is accomplished by a host of different techniques, including standard HHH therapy, ventricular drainage, and more novel invasive techniques that include removal of the craniotomy flap, as well as cerebral angioplasty. Cellular energy demands are minimized during periods of oligemia by hypothermia, seizure prophylaxis, and avoiding hypoxia, acidosis, and hyperglycemia as well as providing neuroprotection.

It is important to note that standard HHH therapy is not without risk, as demonstrated by patients in Cases 20 and 21. Authors of other studies have reported complication rates of pulmonary edema (7-17%), myocardial infarction (2%), coagulopathy (3%), and dilutional hyponatremia (3-35%).[8, 9] Because of underlying cardiac dysfunction, neither of these two patients (Cases 20 and 21) tolerated HHH therapy. The patient in Case 20 developed severe loss of cardiac contractility and rapidly developed cardiac failure at low-filling pressures. The patient in Case 21 sustained a myocardial infarction resulting in electromechanical dissociation and death. When faced with a patient with both poor cardiac function and advanced age, it may be necessary to consider a less toxic therapy than HHH treatment and avoid pentobarbital therapy unless an absolutely life-threatening condition exists. It is also well reported that poor-grade SAH patients have a higher incidence of acute lung injury.[5] The modalities used to treat pulmonary insufficiency may also compromise the treatment of vasospasm (Table 3).

TABLE 3 TREATMENT PROTOCOL	
mission	neurological rescue
threat	danger of irreversible injury from focal ischemic neuronal pool
action	coordinated, rehearsed, rapidly conducted plan of attack with 3 simultaneous objectives
	I reduce ICP
	II improve CBF
	III decrease CMRO ₂
implementation	intubation (avoid hyperventilation < 30) ventriculostomy (drain CSF/intrathecal access) pentobarbital administration (decreases CMRO ₂ /free radical scavenger) early angioplasty (restore CBF in region w/lost autoregulation) decompressive craniotomy (bone flap removal) avoid systemic & metabolic insults (treat/avoid hyperglycemia, acidosis, electrolyte fluctuations, hypoxia, hyperthermia, sepsis, lactate elevation)
* CMRO ₂ = cerebral metabolic rate for oxygen.	

Currently, our trend is toward early performance of angioplasty and use of pentobarbital therapy only when distal spasm predominates in the face of elevated ICP.

Pentobarbital therapy is only one aspect used in the emergency treatment response to symptomatic medically intractable vasospasm. Its use includes rapidly coordinated and rehearsed protocols for restoring CBF. Pentobarbital not only reduces cerebral metabolic oxygen rate[2] until electrical silence is obtained (equating with a 50% decrease in cerebral metabolic oxygen rate), but also enhances the binding of gamma-aminobutyric acid, an inhibitory neurotransmitter, thereby reducing excitotoxicity and increased energy expenditure.[1,4,6,7,9,12,14,15] One of the most important modes of action of pentobarbital is as a free radical scavenger that reduces the lipid peroxidation of the neuronal cell membrane and intracellular organelles.[10,11]

Experience with combined endovascular therapy and pentobarbital is limited. In a recent study,[4] 18 patients with medically intractable vasospasm who underwent endovascular therapy were divided into two equal groups; one group was treated with combined therapy using thiopental, whereas the other group only underwent endovascular therapy. A more favorable outcome was seen in the barbiturate adjunctive group in which five of nine improved to good recovery; one had mild deficit, and one died. These patients also underwent jugular-bulb monitoring, with subsequent improvement in the arteriovenous lactate difference and in cerebral oxygen extraction with restoration of normal coupling of CBF and oxygen consumption. In the control arm, two of nine patients had good recovery, two had mild deficit, four had severe deficit, and one died. The authors concluded that this protocol should be used as a last-line therapy for intractable vasospasm.[4]

Timing and indications for barbiturate protection remain controversial. Proponents of barbiturate protection agree that best results are achieved when burst suppression occurs prior to the ischemic insult. This is not practical for the unpredictable nature of vasospasm. However, it is agreed that beyond 3 hours a deleterious effect is noted in experimental models.[10,11,16] Barbiturate therapy may be replaced by early use of pentobarbital in the face of intractable vasospasm, especially when accompanied by increased ICP or distal spasm not likely to respond to proximal angioplasty. Our results support early (< 2 hours) initiation of pentobarbital therapy before a deficit becomes irreversible.

The neurovascular uses of pentobarbital have included neuroprotection during temporary aneurysm clipping, carotid endarterectomy, hypothermic cardiac arrest, and vascular bypass surgery. Early experience with pentobarbital therapy for the treatment of vasospasm produced poor results. Kassell, et al.,[8] have reported on 12 patients who were treated with high-dose pentobarbital; three of these patients initially benefited, although two of them eventually died, and nine additional patients died as well. The surviving patient was left with paraparesis. Other experiences with pentobarbital therapy and vasospasm are summarized in Table 4. These experiences all have a common element: neuronal protection was established without restoration of CBF. Our experience has differed because of the two-pronged attack to restore CBF and protect the compromised neuronal pool. Integrating reduction of ICP (ventriculostomy and craniectomy) and restoring CBF with angioplasty has resulted in a successful neurological rescue; the lives of 21 of 32 patients have been saved and, most importantly, seven

of these 21 patients have returned to independent living; only eight patients require minimal assistance with daily activities, and four patients are moderately disabled at less than 3 months posthemorrhage. We are encouraged by these results, but we also feel remiss about the two patients who remain vegetative survivors. Their tremendous loss in quality of life and their emotional, financial, and personal devastation have driven us to seek new means to improve outcome with earlier therapies and to pursue new treatment modalities.

TABLE 4			
SUMMARY OF STUDIES IN WHICH PATIENTS RECEIVED BARBITURATE THERAPY IN THE TREATMENT OF CEREBRAL VASOSPASM*			
Authors & Year	No. of Patients	Treatment	Outcome
Hashi & Tanaka,	6	secobarbital 10 mg/kg, 3 patients for 14 days	2 dead, 1 vegetative, 3 improved w/out deficits
Kassell, et al., 1980	12	15-30 mg/kg load, 2 mg/kg/hr maintenance	9 dead; 3 improved (2 died, 1 improved then deteriorated w/paraparesis)
Samsom & Beyer, 1980	7	thiopental < 72 hrs	none improved; 4 dead; 1 vegetative; vegetative; 2 major deficits; 4 patients discontinued, not tolerating drug
Woodcock, et al., 1982	5	pentobarbital	1 (secondary to AVM) improved; 4 died of intractable ICP
current study	32	5-10 mg/kg load 4-6 spikes/min combined w/ICP reduction & angioplasty	21 survivors, 7 return to work, 8 minimal deficit, 4 at home w/moderate assistance w/ADLs, 2 vegetative
* ADL = activities of daily living; AVM = arteriovenous malformation.			

The early use of cerebral angioplasty has provided tremendous gains in the treatment of delayed cerebral vasospasm when it involves proximal cerebral arteries. Eskridge and Song [3] reported the use of balloon angioplasty in more than 150 patients who were typically treated within a time window of 12 to 18 hours. In a selected group of 52 patients, they identified the superior results of balloon angioplasty when compared with papaverine therapy; 39 patients underwent angioplasty and 13 papaverine therapy. Only one vessel of 101 treated in the angioplasty group required retreatment with balloon angioplasty, whereas in the papaverine group 42% required retreatment. The time period for intervention and the pattern of vasospasm (proximal, distal, diffuse) was not specified. In a study of 93 patients who underwent angioplasty, Rosenwasser and coworkers (unpublished data), reported a 70% sustained clinical improvement in 51 patients treated within 2 hours but only a 40% sustained improvement in 33 patients treated after 2 hours. Time and location of spasm play a key role in determining the likelihood of response to endovascular techniques. Distal spasm is the most recalcitrant to endovascular treatment. Although balloon angioplasty is effective in dilating the proximal arteries, papaverine therapy used for distal spasm has a very short half-life, requiring frequent retreatment. The hazards of papaverine therapy are numerous, including crystalization, hypotension, intractable ICP, and hemorrhagic transformation of cerebral infarctions. Currently, no single agent is effective at long-term reversal of distal vasospasm, although there are several agents on the horizon awaiting clinical trials to prove their effectiveness (unpublished data)

In the battle against vasospasm, a rapid, coordinated intervention to protect the neuronal pool and restore blood flow must occur if worthwhile survival is to be attained. Ultimately, the lessons learned from earlier use of pentobarbital therapy demonstrated that when used alone it is not the solution. Restoring CBF and reducing ICP must occur in tandem before a completed infarct occurs. Pulmonary and cardiac complications associated with pentobarbital use should be anticipated and cardiopulmonary function should be optimized with oximetric Swan-Ganz monitoring and early tracheostomy and bronchoscopy for pulmonary toilet. Our experience does support the tailored use of pentobarbital therapy combined with CBF restoration. Despite the best equipment, medicines and expertise, one must race against the clock to salvage an ischemic neuronal pool and avoid the tragedy of patients enduring in vegetative state.

References

1. Belopavlovic M, Buchthal A, Beks JWF: Barbiturates for cerebral aneurysm surgery. A review of preliminary results. **Acta Neurochir** 76:73-81, 1985

2. Cruz J: The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. **Crit Care Med** 26:344-351, 1998

3. Eskridge JM, Song JK: A practical approach to the treatment of vasospasm. **AJNR** 18:1653-1660, 1997

4. Fandino J, Weiser HG, Kraye S, et al: Barbiturate coma for intractable cerebral vasospasm after aneurysmal subarachnoid hemorrhage. **J Neurosurg** 88:192A, 1998 (Abstract)

5. Gruber A, Reinprecht A, Görzer H, et al: Pulmonary function and radiographic abnormalities related to neurological outcome after aneurysmal subarachnoid hemorrhage. **J Neurosurg** 88:28-37, 1998

6. Hashi K, Tanaka K: Barbiturate coma for severe brain ischemia due to cerebral vasospasm, in Wilkins RH (ed): **Cerebral Arterial Spasm**. Baltimore: Williams & Wilkins, 1980, pp 637-645

7. Hoff JT, Nishimura M, Newfield P: Pentobarbital protection from cerebral infarction without suppression of edema. **Stroke** 13:623-628, 1982

8. Kassell NF, Peerless SJ, Drake CG, et al: Treatment of ischemic deficits from cerebral vasospasm with high dose barbiturate therapy. **Neurosurgery** **7**:593-597, 1980

9. Kofke WA, Yonas H, Wechsler L: Neurologic intensive care, in Albin MS (ed): **Textbook of Neuroanesthesia With Neurosurgical and Neuroscience Perspectives**. New York: McGraw-Hill, 1997, pp 1247-1347

10. Nehls DG, Spetzler RF: A review of cerebral protection against ischemia: Part 1. **BNI Q** **2**:1823, 1986

11. Nehls DG, Todd MM, Spetzler RF, et al: A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. **Anesthesiology** **66**:453-464, 1987

12. Piatt JH Jr, Schiff SJ: High dose barbiturate therapy in neurosurgery and intensive care. **Neurosurgery** **15**:427-444, 1984

13. Samson DS, Beyer CM: Thiopental coma in the treatment of vasospasm induced cerebral ischemia/infarction, in Wilkins RH (ed): **Cerebral Arterial Spasm**. Baltimore: Williams & Wilkins, 1980, pp 634-636

14. Selman WR, Spetzler RF, Roski RA, et al: Barbiturate coma in focal cerebral ischemia. **J Neurosurg** **56**:685-690, 1982

15. Smith AL, Hoff JT, Nielsen SL, et al: Barbiturate protection in acute focal cerebral ischemia. **Stroke** **5**:1-7, 1974

16. Traeger SM, Henning RJ, Dobkin W, et al: Hemodynamic effects of pentobarbital therapy for intracranial hypertension. **Crit Care Med** **11**:697-701, 1983

17. Woodcock J, Ropper AH, Kennedy SK: High dose barbiturates in non-traumatic brain swelling: ICP reduction and effect on outcome. **Stroke** **13**:785-787, 1982

Manuscript received August 24, 1998.

Accepted in final form September 24, 1998.

Address reprint requests to: Robert H. Rosenwasser, M.D., 834 Walnut Street, Suite 650, Philadelphia, Pennsylvania 19107.