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ACUTE VASOACTIVE EFFECTS OF
ESTRADIOL ON CEREBRAL VASOSPASM
IN WOMEN WITH SUBARACHNOID
HEMORRHAGE



Joshua Michael Rosenow

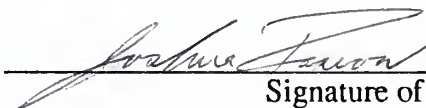
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ACUTE VASOACTIVE EFFECTS OF ESTRADIOL ON CEREBRAL VASOSPASM IN WOMEN WITH SUBARACHNOID HEMORRHAGE. +Joshua M. Rosenow, #Phillip M. Sarrel, +Issam A. Awad, *Lawrence M. Brass. +Section of Neurosurgery, Department of Surgery, and Departments of *Neurology and #Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT.

Approximately a third of patients diagnosed with subarachnoid hemorrhage will develop symptomatic vasospasm leading to delayed ischemic deficits (DID). Estrogen has been shown to either vasodilate or inhibit vasoconstriction in several vascular beds. This may occur by either a calcium channel-blocking effect or via induction of nitric oxide release by vascular endothelium.

We studied 9 women diagnosed with aneurysmal subarachnoid hemorrhage. Estradiol-17 β (E2) and progesterone levels were measured daily. Women received daily monitoring for vasospasm with transcranial Doppler (TCD) ultrasound. Patients whose mean blood flow velocities (BFV) exceeded 120 cm/sec were deemed to be in vasospasm and received E2 1mg SL (Estrace®). TCD monitoring was conducted for 20min prior to E2 administration and for 120 min post-administration. E2 levels were measured prior to and 2 hours after administration of E2.

Three women were given estradiol a total of 4 times early in their hospitalization. Mean BFV showed a statistically significant decrease from baseline beginning at 25 min ($p < .02$) and continuing through the 120 min monitoring period ($P < .005$ at 120min). Mean BFV were not significantly decreased in those trials conducted greater than 6 days post-hemorrhage ($n=2$). There was no significant change in either peak flow velocity or pulsatility index.

This preliminary study demonstrates that estradiol-17 β administration leads to a significant decrease in the mean BFV of women who have suffered a SAH. The effect of E2 is greater and begins sooner when it is given prior to 6 days post-hemorrhage. These early data warrant the further investigation of this finding, including double-blind studies to determine the efficacy of E2 supplementation in preventing vasospasm.

Acute Vasoactive Effects of Estradiol on Cerebral Vasospasm in Women with
Subarachnoid Hemorrhage

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Joshua Michael Rosenow
1996

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Acknowledgments

The author wishes to thank Drs. Issam Awad and Lawrence Brass for their inspiration, enthusiastic support and endless assistance throughout this project. They have nurtured my desire to pursue a career in the neurosciences and the lofty example they have set for me as academic physicians will always provide me with a goal for which to strive.

Dr. Phil Sarrel also deserves thanks for his ongoing encouragement and help. Dr. Philip Dickey assisted with the identification of patients, and his support is greatly appreciated. Dr. Michael Schneck gave technical assistance with the TCD machine and provided valuable advice on the study design. The author would also like to thank the staff of the Neurological Intensive Care Unit at Yale-New Haven Hospital for their aid and patience.

My family deserves special recognition for their dedication to helping me achieve my goals. Without their continual love and support, none of this would have been possible.

Introduction and Purpose

Subarachnoid hemorrhage (SAH) due to the rupture of an intracranial aneurysm presents a serious clinical problem. Up to 50,000 new cases occur in the U.S. each year(110). Delayed cerebral ischemia due to cerebral vasospasm is a major cause of morbidity and mortality, accounting for death or serious disability in an estimated 33% of patients who survive the initial hemorrhage(59).

Current treatment for vasospasm is limited. Induced hypertension and/or hypervolemia are used post-operatively in an attempt to maintain cerebral perfusion pressure during the spastic period. The most widely used pharmacological therapy for prevention and treatment of vasospasm, nimodipine, has had only limited success in either preventing or treating spasm(179). Several outcome studies have failed to show an improvement in post-operative mortality, neuropsychological testing, and return to work in treated patients as compared to controls(58).

Estradiol has been shown to have a vasodilatory effect on constricted arterial beds in several conditions and may have therapeutic potential in cerebral vasospasm. Administration of estradiol leads to increased flow velocity and decreased vascular resistance in normal vessels and in a number of pathologic conditions associated with vasoconstriction or spasm(225, 299). These effects have been shown in the vessels of the leg, forearm, uterus, heart, as well as the brain(36, 38, 218). Middle cerebral artery blood flow in women has been shown to increase in direct proportion to the estrogen level(246). It has been demonstrated that estrogen can enhance the production and release of the endothelial-derived relaxing factor (EDRF) nitric oxide(233). Cerebral vasospasm is associated with

deficient EDRF production and the hemoglobin in the subarachnoid blood efficiently binds nitric oxide(46, 87).

Transcranial Doppler (TCD) ultrasonography, the most common method used to detect vasospasm, is a noninvasive method of recording blood flow velocities of the large intracranial arteries(3). Studies have shown that transcranial Doppler (TCD) ultrasonography is highly specific in the diagnosis of vasospasm(250). High velocities in the middle cerebral artery (MCA) have been correlated with the time course and intensity of delayed cerebral ischemia(95).

Based on this information, we decided to investigate whether estradiol administration could lead to a decrease in the degree of cerebral vasospasm after SAH in women, as measured by transcranial Doppler (TCD) ultrasound. By introducing estrogen as a possible therapeutic tool, our results could help improve the management of subarachnoid hemorrhage in women and may allow the development of novel therapeutic strategies in all patients with subarachnoid hemorrhage.

Chapter 1: Subarachnoid Hemorrhage

Epidemiology of SAH

Stroke is the third leading cause of death in the United States. Stroke in older patients is most often ischemic, as a result of cerebrovascular occlusive disease. However, in younger patients strokes most often have a hemorrhagic etiology. Subarachnoid hemorrhage accounts for about 5% of strokes, yielding almost 50,000 cases per year(110). Moreover, half of hemorrhage survivors are left with a major disability and two-thirds never return to their previous level of functioning(60).

Hemorrhage into the subarachnoid space may be the result of several types of pathology. While the most frequent cause of subarachnoid hemorrhage (SAH) in general is trauma, spontaneous subarachnoid hemorrhage is most commonly due to the rupture of an intracranial saccular (berry) aneurysm. Other etiologies include hemorrhage from vascular malformations, vasculitis, moya-moya disease, or the extension of an intracerebral hemorrhage(22). In as many as 20% of hemorrhages a specific etiology is never defined(174). This discussion will be concerned primarily with SAH of aneurysmal origin.

The mean age at hemorrhage for these patients is 50 years, with approximately 20% of cases occurring in patients between the ages of 15 and 45 years. Approximately 10% of patients die before receiving medical attention and the 30-day mortality rate approaches 50%(29).

Formation of aneurysms

Defects in the arterial wall

It has been estimated from autopsy studies that between 5% and 10% of the population harbor intracranial aneurysms(177, 178, 300). Aneurysms tend to form at the branch points of the cerebral arteries. Aneurysms are most common in the anterior portion of the circle of Willis(187). Almost 90% of aneurysms are present in the anterior circulation, with 30% on either the anterior communicating artery (a-comm) or the anterior cerebral artery (ACA). Approximately 25% are found on the posterior communicating artery (p-comm). Another 20% originate from the middle cerebral artery (MCA) and its branches, frequently at the trifurcation of the M₁ segment. The remainder of the anterior circulation aneurysms are found on the internal carotid artery (ICA), especially at the origin of the posterior communicating artery, or less common sites, such as the ophthalmic artery. In the posterior fossa, the bifurcation of the basilar artery is the most common location for an aneurysm. The posterior-inferior cerebellar artery (PICA) may also be the site of an aneurysm. In a retrospective study, Østergaard found multiple aneurysms in 133 of 748 patients (17.8%)(206).

Histologically normal arterial walls consist of an inner layer of endothelial cells, a layer of intima, a muscular medial layer, and an outer fibrous adventitia. An internal elastic lamina separates the intima from the media and contributes significantly to the overall strength of the arterial wall. No external elastic lamina, such as that in other systemic arteries, is present in the cerebral vasculature.

Defects in the medial layer may be present at arterial bifurcations. In 1930, Forbus termed these areas lacking in musculature "loci minoris resistentiae."

(areas of minor resistance) (78) He believed that this congenital anomaly was the prerequisite for aneurysm development. While these medial defects are usually benign, it has been theorized that when the medial defect is combined with a defect in the internal elastic lamina, the integrity of the wall is compromised. Hemodynamic stress may cause bulging of the endothelium through this region, resulting in aneurysm formation. Unlike normal arterial segments, the aneurysm wall consists only of endothelium, intima, faulty elastica, and adventitia(244). The aneurysm wall is therefore devoid of much of the strength of a normal vessel.

Stehbens, however, has challenged the idea that congenital medial defects must be present for aneurysm formation(258). Examining 311 arterial bifurcations in 117 cadavers, he found that the incidence of medial defects increases with increasing age. However, this does not necessarily indicate that the defects had not already been present since birth. Moreover, aneurysms are not commonly found on small arteries, a common site for medial defects. In addition, he notes that medial defects are also common in extracranial locations rarely associated with aneurysms(259). Instead of a congenital etiology, he theorizes a process of degeneration of the internal elastic lamina, combined with attenuation of the media and variable attenuation of the adventitia. He noted the presence of "funnel-shaped dilatations" and "areas of thinning" with these histological characteristics that occurred at common locations of aneurysms(260).

Collagen defects

Collagen fibers are responsible for much of the load-bearing in the arterial wall. Types I and III collagen predominate in vascular tissue. Type I molecules serve to increase the tensile strength of the wall, while type III

collagen regulates collagen fibril and fiber structure. In the medial layer, these fibers run circumferentially.

Østergaard subjected postmortem specimens from patients with ruptured aneurysms first to mechanical studies and then to electrophoresis in order to determine whether there was a difference in the amount of collagens I and III in these individuals and if that difference altered the mechanical properties of the arteries(203). Six of 14 patients exhibited a deficiency in the type III collagen content of their arterial walls. In addition, these collagen-deficient arteries tended to be more extensible under stresses corresponding to blood pressures between 100 and 200 mmHg than were the arteries from aneurysm patients not lacking collagen type III or those of control patients.

Neil-Dwyer utilized cultures of skin fibroblasts from patients with cerebral aneurysms who were undergoing surgery(188). Radioactive collagen precursors were added to the growth medium to track the synthetic activity of the cells. In cultures from almost half of the patients, a reduced amount of collagen type III was produced by the fibroblasts. This has furthered the theory that an underlying connective tissue deficiency exists in patients with cerebral aneurysms. Moreover, individuals with congenital connective tissue deficiencies, such as those with Marfan's Syndrome, polycystic kidneys, or Ehlers-Danlos Syndrome, are at higher risk for aneurysm formation(14, 165). In fact, it is generally accepted that an insufficiency of collagen type III is present in those patients with Ehlers-Danlos syndrome type IV(161, 226).

Enlargement of aneurysms

Aneurysms may gradually enlarge with time. Pulsatile blood flow has been proposed to exert a "water hammer" effect on the aneurysm wall, thus

exerting a force that progressively expands the sac. Yamaki has shown that the pressure-volume relationship curve is N-shaped(306). The lack of a compliant wall results in a steep increase in pressure as volume slightly increases. At some point, the aneurysm acutely enlarges until a new steady state is reached. Further increases in volume once again result in sharp pressure increases due to the noncompliant wall. This may lead to rupture of the aneurysm, especially at thinner regions of the wall.

Investigations into the association of aneurysms with arteriovenous malformations (AVMs) has furthered theories of aneurysm pathogenesis that focus on hemodynamic factors. Published reports state that between 2.7% and 9.3% of patients with AVMs also have intracerebral aneurysms(20). Since this number is not substantially increased from the incidence in the general population, some have discounted the role of vascular defects in aneurysm formation. Studies analyzing the locations of these aneurysms have noted that as many as 37% to 69% are located on major feeders(53, 107). These feeders are subjected to markedly increased rates of flow and higher levels of hemodynamic stress. Somach and Shenkin reported that ligation of one carotid could result in formation of new aneurysms on the contralateral carotid as well as the anterior communicating artery within 3 to 10 years(254). Shenkin, Hayashi, and others have all published reported of feeding vessel aneurysms decreasing in size after resection of the AVM and normalization of flow(107, 149, 247).

While pressure within the aneurysm may increase the likelihood of rupture, Nornes monitored the epidural pressure in patients whose aneurysms had already bled to investigate the role of extramural pressure forces in controlling rebleeding(193). Rebleeding was successfully controlled when the epidural pressure rose to a level equal to the systemic diastolic pressure. In addition, measures that lowered the epidural pressure (lumbar puncture,

ventricular tap, mannitol administration) all increased the incidence of rebleeding.

Risk Factors

Hypertension as a risk factor for formation, enlargement and rupture of aneurysms

Hypertension has been proposed as a major risk factor for aneurysm formation. A hypertensive rat model produced an increase in the incidence of intracranial aneurysms among those animals. Theorizing that if hypertensive individuals were more at risk for aneurysm formation, they would be also be more at risk for harboring multiple aneurysms, Østergaard compared the hypertensive status with the number of aneurysms in 737 patients with at least one aneurysm(206). Patients with multiple aneurysms were almost twice as likely to be hypertensive (41.3% vs. 21.1%) than patients with a singular lesion.

Unfortunately, due to the large number of cases of undiagnosed hypertension, it is difficult to truly determine the percentage of patients with pre-existing hypertension. Moreover, postmortem studies will be biased by the fact that hypertension increases the mortality rate from subarachnoid hemorrhage(159, 174, 279).

If hypertension is a risk factor for aneurysm formation, then it is a natural extension of this to investigate hypertension as a risk factor for aneurysm rupture. As part of the Framingham Study, 36 of 5184 patients suffered a subarachnoid hemorrhage during the 26-year period of the study(228). These patients had all been followed with biennial blood pressure screenings. Hypertensive disease was present in 50% of patients as compared to 36% of matched control subjects. Bonita conducted a study among New Zealanders that

found that approximately one quarter of hemorrhages could be explained by the presence of hypertension(25).

However even though no studies have been able to show a direct correlation between a hypertensive episode and aneurysm rupture, it is known that events that acutely raise intracranial pressure are associated with hemorrhage. Moreover, despite the improvement in blood pressure control among the general population over the last several decades, the incidence of aneurysmal subarachnoid hemorrhage has remained fairly constant(110, 163). As a result, it remains inconclusive as to whether hypertension is responsible merely for the formation of saccular aneurysms or whether it is also responsible for their rupture.

Smoking as a risk factor

Tobacco use is associated with a higher risk for aneurysm formation. One prospective study involving 118,000 women demonstrated that former smokers had a lower risk of subarachnoid hemorrhage than current smokers and that the duration of cessation was associated with decreasing risk(45). Longstreth investigated 149 cases in King County, Washington over 2 years and found that the odds ratio for heavy (over 1 pack per day) smokers was 11.1(162). In light (less than 1 pack per day) the odds ratio was only 4.1, while former smokers had an odds ratio of only 1.8. In the first 3 hours after a smoking cigarette, the odds ratio for subarachnoid hemorrhage was 7.0. In the Framingham Study, 50% of cases but only 29% of controls had a history of heavy smoking ($p < 0.03$). While both alcohol and smoking are thought to exert their influence through their effects on blood pressure, this remains controversial(228). In fact, Longstreth's study still showed an increased risk among smokers even after controlling for a history of

hypertension. Other studies have consistently shown the association between smoking and subarachnoid hemorrhage(24, 45, 76, 133, 147, 185, 213, 297)

Oral contraceptive use as a risk factor

Conflicting data exist as to the influence of oral contraceptive (OCP) use on the incidence of subarachnoid hemorrhage in women. Thorogood *et al.* performed a case-control study utilizing women less than 40 years of age each matched with 2 controls. The relative risk for hemorrhage was 1.1 for current OCP (not significant) users and 1.6 for those women who had ever used the contraceptives(275). In addition, cases were much more likely to be current smokers. When this was controlled for, the relative risk for current OCP use was 1.3 (nonsignificant), but only 1.0 for those women who had ever used OCPs. This study tended to point away from OCPs as a major contributor to aneurysm rupture. Several other British studies have also failed to find a significant effect of OCP use(221, 292). However, the Royal College of General Practitioners' Oral Contraception Study found a relative risk of 4.0 - 4.5 for subarachnoid hemorrhage among those women who had ever used OCPs(154). The most profound effect was demonstrated by Petitti and Wingerd in their analysis of the Walnut Creek Contraceptive Drug Study(213). Their results indicated that current use of OCPs carried a relative risk of 6.5 ($p < 0.05$) as compared to non-users (controlled for smoking). Moreover, OCP users who smoked had a relative risk of 22 ($p < 0.001$). Smoking alone carried a relative risk of 5.7 ($p < 0.05$). While the influence of OCP use on subarachnoid hemorrhage is still debatable, these studies further defined the risk that smoking carries.

Age as a risk factor

Increasing age is another well-established risk factor for aneurysm formation. Aneurysms in children are rare, but their risk of rupture is higher than those present in adults and the elderly(161, 204, 297). This leads to the idea that these aneurysms are formed via a different mechanism that affects the patient earlier in life. Age has not been shown to correlate with aneurysm size, and previously stated, subarachnoid hemorrhage is most common during the sixth and seventh decades of life(110). As with hypertension, then, age appears to be a definite risk factor for aneurysm formation, but is an uncertain contributor to aneurysm rupture.

Genetic and gender factors

Males seem to be more susceptible to aneurysm formation during childhood and adolescence. However, during adulthood, a female preponderance (approximately 60% to 40%) exists among subjects harboring aneurysms(161, 174, 204). Among the 36 cases of subarachnoid hemorrhage in the Framingham Study population, 22 (61.1%) were women(228). An autopsy study also produced a higher number of women with intracranial aneurysms (7.2% vs. 3.5% of male cadavers)(35). This relationship holds true among patients with both symptomatic and asymptomatic unruptured aneurysms. Women also have a higher incidence of unruptured multiple aneurysms. In Østergaard's population with multiple aneurysms, women constituted 67.6% of the group with 2 aneurysms and 71.4% of the patients with 3 aneurysms(206). This may be due to the genetic propensity of women to develop connective tissue disorders.

Many papers have been published espousing a familial etiology to aneurysm formation(165). Several genetic disorders are associated with intracranial aneurysms. These include the previously mentioned Marfan's Syndrome, polycystic kidneys, and Ehlers-Danlos Syndrome. There have also been many case reports of familial aggregation of aneurysms(105, 224, 231, 297). Lastly, several studies have demonstrated a higher incidence of subarachnoid hemorrhage among identical twins(28, 69, 240, 305).

Norrgård's 1987 study of subarachnoid hemorrhage survivors revealed that 6.8% reported having a blood relative diagnosed with an aneurysm(194). A study comparing the HLA, ABO, Rh, and complement antigens of 474 patients with those of the general population in one region of Sweden found that the cases were more frequent carriers of the HLA-A28 antigen (13.3% vs. 4.6%, $p<0.05$) and less frequent carriers of the HLA-B40 antigen (6.7% vs. 21.2%, $p<0.05$)(195). Østergaard demonstrated that a relative risk for harboring aneurysms of 2.5 exists with the presence of the BfS phenotype and a relative risk of 4.7 exists with the presence of the HLA-DR2 antigen(205). A meta-analysis by Lozano of 177 patients with reportedly familial aneurysms showed that a greater proportion of these patients experience aneurysmal rupture at an earlier age ($p<0.001$)(165).

Presentation, diagnosis, and grading of SAH

Presenting symptoms and circumstances

Classically described by patients as "the worst headache of my life," the headache due to the rupture of an intracranial aneurysm is the most frequent mode of presentation of these lesions(94). The headache begins suddenly, is

unremitting and may be either localized or generalized. The rupture of an internal carotid artery or ophthalmic artery aneurysm can produce pain localized behind the ipsilateral eye. Anterior communicating artery aneurysms may produce a bifrontal headache. Nausea and vomiting frequently occur shortly after the onset of the event. Consciousness is variably affected(19, 178).

Rupture of an aneurysm often occurs during events that acutely raise the intracranial pressure. Exercising or aerobic activity, lifting, straining during defecation, sexual intercourse, and stress have all been associated with the ictus. However, exertion does not invariably precede the hemorrhage. The Cooperative Aneurysm Study reported that while 31% of ruptures occurred during physically or emotionally strenuous activities, as many as 33% of aneurysmal headaches awakened the patient from sleep(141). An increase in subarachnoid hemorrhage during the third trimester of pregnancy has been demonstrated, primarily due to the stress of parturition(57).

In addition to the acute rupture, aneurysms may also become symptomatic due to mass effect as they enlarge. Since aneurysms of the posterior communicating artery are frequently directed upward, they may press on the oculomotor nerve. This usually leads to a non-pupil-sparing third nerve palsy since the pupillary constrictor fibers run in the outer layers of the nerve. This differs from the palsy seen in diabetics due to occlusive vascular disease that affects the central portion of the nerve, thereby sparing the pupillary response. It is not uncommon for this same deficit to be produced by aneurysms of the posterior carotid wall or the basilar artery. Also, any giant aneurysm may act as any other mass lesion in the skull, causing mental status changes, neurological deficits, and possibly seizures.

Warning signs of SAH

Subarachnoid hemorrhage is often portended by various warning signs. At least 25% and as many as 60% of patients will report having experienced a transient sentinel headache in the 2 weeks preceding the hemorrhage. This "warning leak" may be due to either a small hemorrhage or due to the acute expansion of an aneurysm(200). A study by Verweij *et al.* found that the headache frequently lasted as long as several days and was often accompanied by neck stiffness. Most occurred during rest periods. While the outcome for patients who had experienced a warning headache was slightly worse, the difference was not statistically significant(291). Juvela reported that patients with aneurysmal subarachnoid headache recalled a warning headache more frequently than those patients with hemorrhage of unknown etiology (37% vs. 13%, $p < 0.05$). Even though patients who had experienced a warning headache were admitted at a significantly worse clinical grade (Hunt and Hess scale, see below), outcomes, the incidence of rebleeding, or the incidence of delayed ischemia were not different between the two groups(131).

Physical findings after SAH

The headache from a warning leak may be accompanied by relatively short-lived minor neurological deficits, such as a change in visual acuity or a third nerve palsy. These are usually associated with facial pain. Transient ischemic attacks may also occur due to the release of emboli from an aneurysmal thrombus.

While the persistent ictal headache is the most common symptom at the time of presentation, other physical and neurologic findings may be present.

Blood in the subarachnoid space may cause the typical symptoms and signs of meningismus (nuchal rigidity, accompanied by the Kernig and Brudzinski stretch signs are indicative of meningeal irritation). Photophobia may also be present, along with a low-grade fever. As previously stated, an oculomotor nerve palsy may be apparent. Occasionally, increased intracranial pressure from the hemorrhage may result in an abducens nerve palsy(19, 178).

Funduscopy exam may reveal various types of ocular hemorrhages in 20% to 40% of patients. Terson's syndrome is a hemorrhage into the vitreous compartment of the eye, present in approximately 4% of patients(284). This clears spontaneously within one year in the majority of cases. As many as 33% of patients may have subhyaloid preretinal hemorrhages, presumably due to the spread of blood in the subarachnoid space along the optic nerve sheath. These conditions result in visual field deficits and a loss of visual acuity(281).

Grading scales for SAH severity

The most widely accepted grading scale for subarachnoid hemorrhage was developed by Hunt and Hess (see table) and utilizes the initial neurological exam to gauge the patient's prognosis and determine the feasibility of early surgery to clip the aneurysm(121). Hunt and Hess found that the mortality rate for patients admitted at grade I or II was 20%. Given that the mortality rate was significantly greater among the grade II patients as compared to the grade I patients, they concluded that meningeal inflammation represented a serious risk factor when considering surgery. Of the grade III patients, 55% improved to either grade I or II and 34% worsened to lower grades.

Other grading systems have been developed by the World Federation of Neurologic Surgeons (WFNS) Committee on a Universal SAH Grading Scale

and the International Cooperative Aneurysm study. The Cooperative Study reported that the most important prognostic factors were the patient's level of consciousness, which had predictive value for death and disability, and the presence of hemiparesis/hemiplegia or aphasia, which only provided prognostic value for disability. In addition, there was no significant difference in outcome between patients in Hunt and Hess grades I and II, as long as consciousness remained normal. The WFNS scale is instead based on the Glasgow Coma Scale score as well as the presence or absence of these deficits. Grades II and III are differentiated by the presence of deficit in patients classified as grade III(61).

Findings on imaging studies

The mainstay of diagnosis of subarachnoid hemorrhage is the unenhanced CT scan. Within the first 48 hours following the hemorrhage, CT scan has the ability to detect over 95% of cases(4, 139). After this time period, the blood tends to become isodense

Grade I	Asymptomatic or minimal headache
Grade II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion, or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity, and vegetative disturbances
Grade V	Deep coma, decerebrate rigidity, moribund appearance

Figure 1: Hunt and Hess Grading Scale for Subarachnoid Hemorrhage

Grade	GCS Score	Motor Deficit
I	15	absent
II	14-13	absent
III	14-13	present
IV	12-7	present or absent
V	6-3	present or absent

Figure 1a: WFNS Grading Scale for Subarachnoid Hemorrhage

with the brain parenchyma, making detection more challenging. The epicenter of the subarachnoid blood may serve as a guide to the aneurysm. Additionally, intravenous contrast may aid in the identification of the location of the aneurysm. CT scan may reveal an aneurysm prior to hemorrhage by detecting calcifications within the wall of the aneurysm.

Intracerebral hemorrhage is present on 20% to 40% of initial scans, and is frequently associated with the rupture of MCA aneurysms.

Intraventricular hemorrhage may result as the consequence of extension of this blood. Hemorrhage from PICA aneurysms one of the more common etiologies of intraventricular blood(94).

In the presence of a negative CT scan but a high degree of clinical suspicion, a lumbar puncture may serve as the next step in diagnosis in those patients not at highest risk for increased intracranial pressure. Direct examination of the cerebrospinal fluid (CSF) is the most sensitive test for subarachnoid hemorrhage. Unlike in the case of a traumatic puncture, the blood in the CSF will not clear with successive tubes. Xanthochromia is present in 90% of all cases of SAH by 12 hours after the hemorrhage. The opening pressure will also usually be elevated(94).

Magnetic resonance imaging (MRI) may add diagnostic information in patients being evaluated a substantial period of time after the suspected

hemorrhage. MRI is more useful in detecting older blood (one week or more) with a higher content of methemoglobin than is CT. There are doubts regarding the ability of MRI to adequately detect acute blood. MRI has also been reported to be of value in identifying the site hemorrhage in patients with multiple aneurysms(10, 125, 187, 197).

Cerebral angiography is the definitive method for localizing the origin of the hemorrhage, as well as providing information regarding the size, orientation, complexity, and morphology of the aneurysm, its neck, and the surrounding vasculature. These characteristics are all critical in planning the clipping or endovascular treatment of the aneurysm. It also allows the detection of angiographic (rather than clinical) vasospasm. A complete four-vessel study is usually performed to rule out the presence of multiple aneurysms or other vascular malformations. As many as 20% to 25% of angiograms will be negative. Repeating the study after a delay of a week will allow the detection of a previously occult aneurysm in 10% to 20% of initially negative cases(42, 80, 88). As software improves, magnetic resonance angiography (MRA) will play an increasingly important role in identifying aneurysms(13).

Management of SAH

Preventing rebleeding

The initial management of patients who have been diagnosed with subarachnoid hemorrhage is aimed at preventing further hemorrhage. Rebleeding may be an acute, devastating complication of aneurysmal subarachnoid hemorrhage, with a fatality rate of approximately 70%(130). The Cooperative Aneurysm Study demonstrated that the rate of rebleeding is 4.1%

with the first 24 hours and 19% within the first 2 weeks. It then declines to 1% to 2% per day for the first month after the hemorrhage(138). Richardson has shown that this is an approximately 30% cumulative rate over the first month with conservative therapy(223). The rate of acute rebleeding is increased by such factors as delay in diagnosis and treatment, elevated blood pressure, and neurological status on admission. The long term rate of rebleeding from an untreated aneurysm has been estimated at 3% per year(124, 223). Risk factors for rebleeding include worse clinical grade, large aneurysm size, and preexisting medical conditions(113, 251, 279).

To minimize the chance of rebleeding, strict precautions are taken. The patient is kept in a quiet, darkened room in an intensive care setting. Antihypertensives are utilized to prevent large swings in systolic blood pressure that could precipitate rebleeding. However, there has yet to be conclusive evidence that antihypertensives prevent rebleeding(174). Medications, such as nonsteroidal anti-inflammatory drugs, are given for pain. Stool softeners are usually given to prevent straining. Seizure and vasospasm prophylaxis are usually initiated (see below). Patients who cannot adequately protect their airway or who require hyperventilation for intracranial pressure control are intubated. Arterial lines and pulmonary artery catheters may be used in unstable patients who require close hemodynamic monitoring. If the patient's clinical condition permits, preparations for surgery are made(19, 178).

Hydrocephalus associated with SAH

Hydrocephalus may result acutely from obstruction of the ventricular system. The obstruction is most probably at the level of the outlet foramina of the fourth ventricle. However, extension of the hemorrhage to the ventricular

system may also cause blockage of CSF flow through the foramen of Monro or the aqueduct of Sylvius. It has been reported to occur in 20% to 27% of cases of subarachnoid hemorrhage(174, 181). Affected patients are usually of a lower clinical grade than those without ventriculomegaly. Ballooning of the frontal horns of the lateral ventricles has been reported to be the earliest change detectable by CT scan(94).

Chronic hydrocephalus (1 month after the hemorrhage) has been reported to occur in as many as 60% of patients(23), but most commonly in the range of 14% to 23% of cases(160, 288). The most likely etiology is a blockage of CSF flow at the arachnoid granulations. These patients may require permanent shunt placement.

A patient with acute hydrocephalus is a candidate for ventricular drainage to alleviate the increased intracranial pressure. However, the role of ventricular drainage in promoting aneurysm rerupture is still controversial. Theoretically, bleeding from the aneurysm is tamponaded by the intracranial pressure. By decreasing this force, ventricular drainage may lead to an increase in the transmural gradient from within the aneurysmal sac, causing rebleeding. Many studies, though, have failed to define a statistically significant relationship. Voldby and Enevoldsen reported that draining CSF only at pressures greater than 25 mmHg produced no increase in the rate of rebleeding(294). Paré *et al.*, though, found that ventricular drainage was associated with an odds ratio of 5.31 ($p < 0.05$) for rebleeding(209).

Antifibrinolytic therapy

Antifibrinolytic therapy was first introduced in the late 1960s as a method of reducing the probability of rebleeding by preventing breakdown of any clot

that might be sealing the tear in the aneurysm. Epsilon aminocaproic acid (36 g/day) or tranexamic acid (6 to 12 g/day) are the compounds most frequently used for this purpose(174). The Cooperative aneurysm study found that at 14 days post-hemorrhage, 11.7% of treated patients had rebled versus 19.4% of controls (a 40% reduction in the incidence of rebleeding). However, delayed ischemic deficits were more significantly common in the treatment group (32.4% vs. 22.7%). Presumably this due to reduced clearance of subarachnoid clot and/or fibrin microemboli. As a result, the overall 30-day mortality rate for the 2 groups did not significantly differ(230). Similar results have been reported by other investigators(140, 280). Currently antifibrinolytic therapy is reserved for patients of low clinical grade who are not candidates for early surgery or who have a low risk of developing delayed ischemia.

Seizures

Seizures have been reported in approximately 25% of subarachnoid hemorrhage patients(268). The use of prophylactic anticonvulsants, however, remains of indeterminate value. While nonrandomized studies have shown that craniotomy patients in general benefit from seizure prophylaxis, no benefit has been found specifically for those patients with subarachnoid hemorrhage. Due to the risk of rebleeding during a seizure, prophylactic anticonvulsants are routinely utilized pre- and peri-operatively despite inconclusive clinical trials(174, 178).

Vasospasm

Cerebral vasospasm, the delayed narrowing of the large arteries at the base of the brain, is the most serious long-term complication of subarachnoid hemorrhage. The prophylaxis, treatment, and possible etiologies of this condition will be thoroughly discussed in a later chapter.

Hyponatremia

Hyponatremia may be present in 10% to 34% of patients with subarachnoid hemorrhage. It first develops 3 to 5 days after the hemorrhage and is more common in patients of lower clinical grade(253). It is still debated whether this is due to "cerebral salt wasting" and possible elevation of atrial natriuretic peptide (ANP) leading to volume contraction or SIADH(189).(6, 150) Weinand, *et al.* found elevated levels of ANP in the presence of normal or low levels of antidiuretic hormone (ADH), leading to the conclusion that natriuresis, rather than inappropriate ADH secretion, is responsible for the hyponatremia(298). Fluid restriction in this setting may lead to exacerbation of this volume depletion and an increased rate of ischemic complications(253, 301). Close monitoring of the patient's sodium level along with the use of isotonic fluids is recommended to prevent excessive contraction of the intravascular compartment.

Involvement of the pituitary gland and the resulting loss of ADH secretion can lead to hyponatremia via diabetes insipidus.

Cardiac complications of SAH

Subarachnoid hemorrhage may cause a variety of cardiac changes. It has been reported that between 50% and 70% of patients show electrocardiographic (EKG) changes. Pathological Q waves, prominent U waves, prolongation of the QT interval, and broadening of the T wave have all been described in association with the hemorrhage. Potentially fatal arrhythmias, such as Torsades de Pointes, may arise due to these effects. An increase in catecholamines leading to raised sympathetic tone is believed to be the mechanism at work(178).

Chapter 2: Cerebral Vasospasm

Cerebral vasospasm results in morbidity or mortality in a third of patients with subarachnoid hemorrhage. Research aimed at identifying the "spasmogen" responsible for this condition has shown many compounds and process can cause spasm by impairing endothelium-dependent vasodilatation, with hemoglobin playing the most prominent role. Current treatment for spasm is limited, utilizing induced hypertension and hypervolemia in combination with calcium channel antagonists.

History and Epidemiology

Early experimental observations

Spasm of the large arteries at the base of the brain after spontaneous subarachnoid hemorrhage was first demonstrated angiographically by Ecker and Riemenschnieder in 1951(63). They noted narrowing of the contrast column on angiograms in 7 of 34 patients. The spasm was more severe ipsilateral to the aneurysm. The internal carotid, middle cerebral, and anterior cerebral arteries were each involved. No spasm was noted on angiograms performed greater than 26 days post-hemorrhage. While they recognized the probable importance of their finding, they did not understand the mechanism. Stating "Strange as it may seem, the normal functioning of the smooth muscle in the walls of the larger arteries has never been elucidated," they hypothesized that spasm represented a "reactive contractile force" that prevented widening of an aneurysmal tear.

In 1965, Echlin noted, in monkeys, that placing autologous blood on the basilar artery once the subarachnoid space had been opened "consistently caused almost immediate, widespread, marked vasoconstriction of all exposed arterial vessels."(62) Blood flow in the affected vessels decreased markedly. The respirations of several of the animals ceased within a few minutes of the onset of vasospasm, thus providing evidence of the devastating consequences of this phenomenon.

Diagnosing vasospasm and incidence

Vasospasm is the most significant cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage, especially after surgery (19, 59, 60, 94, 163, 166, 174, 178, 216, 302). Vasospasm may be defined clinically or angiographically. Angiographic vasospasm refers only to the radiological narrowing of the contrast column in the cerebral vasculature and may be asymptomatic. Symptomatic, or clinical, vasospasm is inexactly defined as a delayed focal ischemic neurological deficit following subarachnoid hemorrhage. Precise criteria have not been defined and the diagnosis is often one of exclusion. New areas cerebral infarction may be found on CT scan, but imaging is not required to satisfy the clinical definition.

Angiographic studies have reported widely ranging estimates of the incidence of spasm (19% to 97%). A large meta-analysis of 223 reports (31,168 patients) stated the incidence to be 43%(59). Kwak and Niizuma reported the incidence to vary between 21% and 62%(152). Spasm was almost never observed earlier than 2 days after the hemorrhage. Onset is most commonly quoted to be around day 4 with the largest number of cases being observed at day 7. During

the second week post-hemorrhage, spasm has been noted on angiogram in an average of 67.3% of cases(59).

The clinical manifestations of vasospasm are less commonly observed. Pooling 297 references, Dorsch and King found 10,445 cases of delayed ischemic deficits among 32,188 patients, for an incidence of 32%(59). However, common criteria for vasospasm were lacking among these reports. For example, some reports did not specify that other causes of neurological deterioration were ruled out and some reports required angiographic confirmation for spasm after development of a neurological deficit. Utilizing only those studies with firm rules for defining symptomatic spasm, they found the incidence to be similar, 32%. Results from other studies have agreed with this figure(15, 25, 146, 157, 163).

Presentation of clinical vasospasm

The effects of vasospasm may first be noticed as a change in the patient's vital signs. A low-grade (not much greater than 39°C) fever has been reported to precede any neurological changes by several days. Ishiguro *et al.* found 62% of patients with an elevated temperature developed clinical spasm, as opposed to only 33% of those patients without fever(123). It is believed that the fever is the result of meningeal inflammation from the hemorrhage(15). The hemorrhage may also affect the hypothalamus, disturbing somatic temperature regulation. It follows logically that patients exhibiting a fever of this origin most likely have more blood in the subarachnoid space and are, therefore, more likely to develop clinically significant vasospasm (as described below). Tachycardia may accompany the fever.

Neurologic deficits may begin insidiously, with only subtle signs such as a slight pronator drift serving as a clue. Several reports note that alterations in consciousness are among the earliest evident changes(74, 108). The patient may appear drowsy and disoriented or may even become obtunded. Focal signs depend on the vessel(s) involved. Spasm of the anterior cerebral artery may result in weakness of the contralateral lower limb, but may also cause frontal lobe findings such as abulia, incontinence, "release signs", and mutism. Middle cerebral artery spasm may lead to contralateral hemiparesis and possibly aphasia (if the spasm occurs in the dominant hemisphere). Spasm of the posterior cerebral artery, associated with aneurysms of the basilar artery, has been reported to result in a syndrome of bilateral ptosis, poor memory, obtundation, and visual field deficits or neglect(15, 19, 74, 94, 108).

Predictive methods for vasospasm

Fisher *et al.* demonstrated the predictive value of early CT scanning for the later development of vasospasm(75) (see figure). Patients were grouped according to the amount of blood present on early (day 1 or 2 post-bleed) CT scans. All of the cases of severe angiographic spasm and all of the cases of clinical spasm occurred in patients whose scans showed localized clot or a vertical layer of blood greater than 1mm thick. While 23 of 24 cases satisfying this criteria experienced severe spasm, only 1 of 18 patients without clot or a 1mm thick layer developed severe spasm. Hirashima *et al.* defined a "total blood score" obtained by grading the amount of blood in each of 10 cisterns from 0 to 3 as noted on CT scan and summing the grades(114). They found that patients who went on to develop delayed infarcts had a significantly higher total blood score on admission

as well as post-operatively ($p < 0.001$ for both). There have been several other reports that corroborate this correlation.

Group 1	No subarachnoid blood
Group 2	Diffuse subarachnoid blood without clots
Group 3	Clot or vertical layer of blood 1mm thick or greater
Group 4	Diffuse or no subarachnoid blood but intracerebral or intraventricular hemorrhage

Figure 2: Fisher CT Grading Scale for Subarachnoid Hemorrhage

Graf and Nibbelink found a correlation between the patient's initial clinical grade as measured by the Hunt and Hess scale and the probability of developing a delayed ischemic deficit(92). Only 22% of grade I patients developed deficits. However, 53% of grade III patients and 74% of grade V patients went on to suffer this consequence.

Effect of vasospasm on outcome after SAH

Spasm results in an increase in death and disability from subarachnoid hemorrhage. Numerous reports have documented the increase in mortality after subarachnoid hemorrhage related to the development of vasospasm. In an analysis of 6098 patients, of which 3482 developed clinical spasm, the odds ratio for death was 3.28 (95% CI 2.94-3.66) when spasm was present. Of these patients, 30.6% of those in spasm died while only 16.6% of unaffected patients died.

Regarding disability, combining 21 studies that utilized the Glasgow Outcome Scale, Dorsch and King found that the odds ratio for a good recovery were 3.05 (95% CI 2.73-3.40) in the absence of spasm. They also performed a further meta-analysis of 197 papers regarding outcome after aneurysmal rupture. Of the 3327 patients included, 30.3% died, 34.0% were left with "permanent deficits", and 35.7% had a "good outcome." Clearly, vasospasm can have disastrous effects on a patient's prognosis after subarachnoid hemorrhage(59).

Alterations in the spastic vasculature

In 1964, Crompton published a landmark description of histologic studies of cerebral arteries taken at autopsy from patients who had died several weeks after a subarachnoid hemorrhage(52). He described not vasoconstriction, but an "arteriopathy." Fibrosis was present, as well as infiltration of lymphocytes and macrophages into the subendothelial space. Some arteries exhibited inflammatory changes in the adventitia as well as necrosis of the media. However, there was controversy as to whether these changes were the result of the hemorrhage or due to pre-existing disease such as hypertension or atherosclerosis. Moreover, since it is considered safe to operate on patients several weeks after their hemorrhage, the question became whether these changes were of any importance in delayed ischemia, which peaks at an earlier time.

Other investigators have obtained similar histological results(119, 175). In addition, they have shown that the medial fibers, as well as the elastica, may be degenerate in spastic vessels. An aseptic inflammatory reaction has been observed in the adventitia, along with edema. Hughes demonstrated that these arterial segments had a reduced internal diameter but an enlarged external

diameter(120). The increased wall thickness was due to intimal thickening and fibrosis, even in the presence of a degenerate intima.

Espinosa, *et al.* performed electron microscopy on vessels removed from monkeys after experimental inducement of spasm by clot placement within the circle of Willis(68). Compared to control arterial segments, the endothelium in the arteries exposed to the hematoma was convoluted. Deep corrugations were present. Some endothelial cells were found to be swollen and vacuolated with disruption of tight junctions. Some smooth muscle cells were in spasm and some contained lysosome-like structures. The adventitia was noted to be irregular and wavy with an infiltrate of erythrocytes, macrophages, plasma cells and leukocytes. Results from other groups have confirmed these changes(175).

Pathogenesis - the role of the endothelium

In recent years the vascular endothelium has been found to play a significant role in many physiologic processes, especially that of regulating vascular tone. In the cerebral circulation, this is extremely important for autoregulation and the maintenance of cerebral perfusion pressure. The cerebral arterial bed is one of several systems, including the renal and coronary circulation, that must keep the blood supply to the organ within very specific parameters. This is accomplished via the interplay of a number of substances both produced and regulated by the endothelium.

Endothelium-dependent vasoconstriction

The endothelium has been proven to be involved in vasoconstriction in response to certain stimuli. Katusic and Vanhoutte reported the ability of

hypoxia to contract isolated cerebral arteries(143). This finding is surprisingly contrary to what one would expect. In most vascular beds, hypoxia leads to vasodilatation

Prostaglandins, especially thromboxane A₂ (TXA₂), have also been implicated in the development of vasospasm. Thromboxane A₂ is a powerful promoter of platelet aggregation. Moreover, it has been shown to cause rapid vasoconstriction of cerebral arteries(199). However, clinical trials of TXA₂ synthesis inhibitors have been inconclusive. A few reports have shown a decrease in delayed cerebral infarcts in patients given TXA₂ synthetase inhibitors(272, 277). Juvela reported a series of 291 patients, of which 37% developed delayed cerebral ischemia(132). He found that those patients with a positive urine test for salicylates on admission had a relative risk of 0.21 (95% CI, 0.03 to 1.63, p=0.14) for delayed neurologic deficits. Aspirin use within 24 hours of admission was associated with a significantly lower risk of developing a fixed deficit (p<0.02). However, of the group studied by Yano, *et al.*, 62% of patients given Xanbon, a TXA₂ synthetase inhibitor developed delayed infarcts, a figure much above even the expected incidence(307). Because thromboxane production is irreversibly inhibited by aspirin, new platelets must enter the circulation for production to recover. This does not occur to a noticeable extent for almost 10 days.

Aspirin infusion prior to the experimental induction of subarachnoid hemorrhage is able to reduce the level of spasm produced in several animal models(132). In a comparison of NSAIDs, aspirin provided the greatest level of protection, presumably due to its potent inhibitory effect on eicosanoid production. Importantly, since platelets (producers of TXA₂) are permanently disabled by aspirin due to their inability to synthesize new proteins, as opposed to endothelial cells (producers of prostacyclin), aspirin treatment shifts the balance

of eicosanoids towards prostacyclin and, therefore, vasodilation. Unfortunately, as noted before, any clinical benefits of TXA₂ inhibitors are still unproven.

In the late 1980s, the first descriptions of endothelin (ET) were first published. Three forms (ET-1, ET-2, ET-3) have been described. This 21-amino acid peptide is the most potent constrictor of cerebral arteries and is effective when applied to the adventitial side of arteries(93). It has been proposed that they act via protein kinase C and intracellular calcium release(216). Hirose, *et al.* demonstrated that intracisternal injection of BQ-123, an endothelin_A (ET_A) receptor antagonist, in normal dogs produced a 29.4% increase in the angiographic diameter of the basilar artery(115). In addition, intracisternal BQ-123 reduced the amount of angiographic narrowing from 42% to 20.8% ($p < 0.05$) 6 days after experimental induction of subarachnoid hemorrhage in these dogs. Clozel and Watanabe duplicated these effects in a rat hemorrhage model, as did Cosentino, *et al.*, in another dog model(44, 49). Nirei, *et al.* reported similar results with the ET_A antagonist FR 139317(191). Serial measurements of CSF levels of ET-1 and ET-3 performed by Seifert, *et al.* in 22 patients revealed that patients who did not develop spasm tended have progressively lower levels of endothelins(242). These levels remained elevated or increased in patients who went into vasospasm ($p < 0.001$). Interestingly, these levels directly correlated with the patient's Fisher grade ($p = 0.05$). The time course of any increase in endothelins correlated with the development of spasm.

However, there has been some controversy as to the true importance of endothelins in subarachnoid hemorrhage. Gaetani, *et al.* published a series of 55 patients that detected no association between cisternal levels of endothelins and spasm(86). Haman, *et al.* and Greenberg's group have both published data that also discounts any association(93, 98).

Endothelium-dependent relaxation

In contrast to its role in vasoconstriction, the endothelium has also been shown to have a significant role in vasodilation(285). The endothelium constitutively synthesizes the eicosanoid vasodilator prostacyclin. Moreover, it releases nitric oxide, the endothelium-derived relaxing factor (EDRF), in response to a variety of stimuli.

It has been proven that the vasodilator prostacyclin (PGI₂) is synthesized and released by the vascular endothelium. Moreover, the neurogenic peptides substance P, vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP) have all been shown to produce dilation of the cerebral vasculature that is not reversible or inhibited by cholinergic or other antagonists(216). Immunocytochemistry has revealed that levels of these peptides gradually decrease in patients who are diagnosed with subarachnoid hemorrhage(282). Juul, *et al.* found that both serum and CSF levels of CGRP were significantly elevated in subarachnoid hemorrhage patients as compared to controls(129).

Endothelium-derived relaxing factor (EDRF), identified as most probably nitric oxide (NO), is presumed to play a central role in mediating endothelium-dependent relaxation of smooth muscle in the cerebral vasculature(9). Ligand-receptor binding at the luminal surface of the endothelial cell leads to activation of the phosphatidyl inositol second messenger system. The inositol triphosphate (IP₃) released leads to an increase in the level of intracellular calcium. This, in turn, activates NO synthase (NOS), causing the production of NO from L-arginine. The NO produced then diffuses into the smooth muscle cells, where it leads to activation of guanylate cyclase. Cyclic guanylate monophosphate (cGMP) is theorized to activate a protein kinase that causes relaxation of the smooth

muscle via phosphorylation of an unknown substrate. Vasopressin and acetylcholine (ACh) are believed to cause endothelium-dependent relaxation of vascular smooth muscle via this mechanism, as is A23187, a calcium ionophore that causes the release of calcium from intracellular stores(9, 216, 285).

It has been proposed that smooth muscle contracts in post-hemorrhage vasospasm due to phosphorylation of myosin light chains by calcium-calmodulin-activated myosin light chain kinase (MLCK). This is spurred by an increase in intracellular calcium through voltage-gated channels in the smooth muscle cells, presumably the result of vascular damage(264). However, while there is a rise in the amount of phosphorylated myosin light chains early in the course of vasospasm (days 2-5 post-hemorrhage), this soon decreases to undetectable levels(101). Calmodulin antagonists have not been shown to have any therapeutic value in countering spasm, suggesting that calcium-dependent contraction is only an acute phenomenon(211, 232). Spasm is postulated to be sustained by activation of protein kinase C (possibly by the same increase in intracellular calcium) which leads to the phosphorylation of other cellular proteins. Phorbol esters, which greatly enhance protein kinase C activity, can produce sustained contractions of canine basilar artery(222). Shibuya reported that AT877, a protein kinase C antagonist, could produce improvement in vasospasm in humans(248).

Impairment of the NO pathway is believed to be associated with the development of vasospasm after aneurysmal subarachnoid hemorrhage. Hirose, *et al.* administered N^G-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NOS, to dogs and produced a 19.3% mean decrease in the basal angiographic diameter of the basilar artery(115). L-Arginine, the precursor of NO, significantly reduced this effect. Moreover, in the two-hemorrhage canine model where experimental dogs receive 2 intracisternal injections of autologous blood several

days apart to mimic the effects of spasm on the human vasculature, L-arginine was able to attenuate the decrease in angiographic narrowing of the basilar artery 4 days post-hemorrhage from a mean decrease of 30.9% of baseline to only 12.6%. Afshar, *et al.* utilized a primate model of vasospasm and demonstrated several effects of the direct ICA infusion of NO(5). Arteriographic narrowing resolved almost completely. In addition, cerebral blood flow increased by 19% without significant changes in mean arterial blood pressure or heart rate. In another study, western blots of segments of basilar artery removed from dogs 7 days after experimental subarachnoid hemorrhage revealed that the level of soluble guanylate cyclase was significantly reduced(142). There was also a decrease in the level of NOS, but it did not reach statistical significance.

Oxyhemoglobin as a spasmogen

Given that the likelihood of spasm developing is directly related to the amount of blood surrounding the cerebral vasculature(75), many investigators have looked to blood as the source of the "spasmogen." Importantly, the previously noted experiments conducted by Echlin demonstrated that the application of blood to the vasculature could cause spasm. Moreover, valid animal models of cerebral vasospasm have been developed using dogs, cats and monkeys, and rodents. Vasospasm is induced via either experimental subarachnoid hemorrhage (intravascular arterial puncture), or by performing a craniotomy and directly placing autologous clot around the circle of Willis(5, 49, 62, 170, 289).

Erythrocytes in the subarachnoid space become hemolyzed, releasing oxyhemoglobin (OxyHb) into the subarachnoid space. Over the course of several days, this is oxidized to methemoglobin (MetHb)(17). Various fractions of blood

have been tested for the ability to induce spasm. Serum, platelet-rich plasma, and erythrocyte lysate have all been shown to cause vasoconstriction. However, incubating the serum or lysate for several days destroyed this ability(167). In numerous papers, xanthochromic CSF has been shown to have the potential for inducing arterial constriction(8, 26, 201).

OxyHb mediation of vasoconstriction

OxyHb itself has been demonstrated to act as a vasoconstrictor in many isolated preparations of animal vasculature(31, 77, 117, 136, 172, 175, 202). Macdonald, *et al.* conducted a controlled, randomized study of the effects of multiple intrathecal injections of various potential spasmogens in cynomolgus monkeys(170). They reported that injections of OxyHb produced significant angiographic vasospasm 7 days after injection. MetHb did not produce this response, nor did mock CSF. One of the OxyHb animals developed an ipsilateral MCA infarct. Histological examination of the contracted vessels from this animal revealed changes consistent with cerebral vasospasm. The intima and endothelium were convoluted and the vessel wall was thickened. Endothelial and smooth muscle cells showed vacuolization. Mayberg *et al.* conducted similar experiments in a pig model(175). In that report, hemoglobin directly applied to the MCA for 10 days produced vasospasm with the characteristic pathology. Whole blood and erythrocyte cytosol, produced similar results while erythrocyte membranes, leukocytes, and platelet-rich plasma did not have this effect.

The mechanism through which OxyHb causes vasoconstriction has not been fully explained. There has been one report of hemoglobin causing an increase in intracellular levels of inositol triphosphate(296). OxyHb-induced

spasm has not been shown to be reversible by the use of many receptor antagonists and second messenger inhibitors. Atropine, phentolamine, propranolol, angiotensin, theophylline, quinine, and other materials have all been used unsuccessfully(167, 302). While calcium channel antagonists have been demonstrated to relax vessels *in vitro*, this has not been borne out in *in vivo* studies in either monkeys or humans(7, 67, 214). However, it has been possible to demonstrate the effects of OxyHb on many of the endothelial cell functions previously described.

The vasoconstrictive effects of several substances are enhanced by treatment of the vessel with OxyHb. For example, Nakagomi and colleagues showed that hemoglobin treatment greatly augmented the contractile response of canine basilar artery segments to hypoxia. This effect was greater than that evoked by either potassium or PGF_{2a}. Even though the association of endothelins and vasospasm is controversial, OxyHb has been shown to increase the release of endothelin from cultured cell lines.

As mentioned earlier, the eicosanoids have both vasodilatory (prostacyclin) and vasoconstrictive (TXA₂) effects on the cerebral vasculature. Tokoro (278) found that OxyHb decreased prostacyclin production by the endothelium without effecting levels of TXA₂. Even though, as stated earlier, several studies document the efficacy of NSAIDs in experimental models of subarachnoid hemorrhage, there have been many reports that document either little or no substantial effect on vessels that have been contracted with OxyHb itself(84, 273, 276).

One of the pathological characteristics of vessels contracted by the application of OxyHb is the degeneration of the nerve endings in the adventitia. These terminals contain the vasodilatory peptides VIP, CGRP, neuropeptide Y (NPY) and substance P. Immunohistochemical studies by Uemura *et al.* have

documented decreased amounts of these peptides present in the adventitia of the middle cerebral and basilar arteries after experimental subarachnoid hemorrhage(282). It is theorized that the loss of these peptides tips the balance of vasoactive forces further towards vasoconstriction.

OxyHb and the NO system

The relationship between OxyHb and NO has been extensively investigated, given the apparently central role of each in the development of cerebral vasospasm. OxyHb binds NO with 1,500 times the affinity of that for oxygen(87). Foley *et al.* reported that Hb is able to penetrate the arterial wall(77). Using basilar arteries removed from rabbits after induction of subarachnoid hemorrhage they were able to demonstrate that the Hb was frequently found in the adventitia but was also commonly present in the smooth muscle layer and even occasionally as deep as the endothelium. This would easily allow OxyHb to interfere with the diffusion of NO from the endothelium to the smooth muscle cells. Kim has demonstrated that only the effects, and not the production, of NO may not be inhibited by OxyHb(144). However, this result has been disputed by conflicting papers(70, 83, 117, 202).

Many papers have documented the ability of OxyHb to inhibit endothelium-dependent relaxation(31, 77, 83, 167, 170, 172, 186). Kanamaru *et al.* demonstrated that OxyHb produced a dose-dependent inhibition of vasodilatation induced by A23187(136). This effect was reproduced by CSF samples taken from patients with subarachnoid hemorrhage, with the greatest inhibition caused by the CSF with the highest concentration of OxyHb. The relaxation induced by papaverine, which does not act via the endothelium, was not affected by treatment with OxyHb.

Several papers have shown that OxyHb can even alter vascular reactivity to the point that substances that previously had acted as relaxants cause contraction of the vessels. This has been demonstrated using ACh, substance P and TRK-100 (a prostacyclin analog)(83, 202).

Martin, *et al.* correlated vascular tension measurements with quantitative changes in the levels of cyclic nucleotides in aortic rings relaxed by treatment with either A23187, glyceryl trinitrate, or isoproterenol(172). Both the calcium ionophore and the nitrate caused an increase in the level of cGMP and a decrease in vascular tension. However, the addition of 10 μ M hemoglobin abolished both of these effects. Isoproterenol-induced relaxation, which is not accompanied by an increase in the cGMP level, was not affected by hemoglobin.

There has been some controversy about the ability of extraluminal OxyHb to inhibit endothelium-dependent relaxation. Many of the previously mentioned papers successfully demonstrated this effect. Hongo found that the intraluminal application of hemoglobin produced a significantly greater effect than extraluminal application(117). However, immunohistochemical studies demonstrated the penetration of extraluminal hemoglobin into the smooth muscle layer, while intraluminal hemoglobin did not penetrate the endothelium. Tanaka and Chiba also reported that when applied in the same concentrations, intraluminal OxyHb had a significantly greater inhibitory effect than did extraluminal OxyHb(270).

The oxidant methylene blue also has the ability to prevent endothelium-dependent relaxation(96). It is believed that this compound oxidizes the heme element of guanylate cyclase so that it is unable to bind EDRF and thus remains unstimulated. As previously stated, OxyHb effectively binds EDRF as well as preventing EDRF-induced relaxation. This observation that other heme-containing proteins do not bind EDRF effectively when oxidized(51, 171) allows

us to connect the fact that MetHb, the oxidation product of OxyHb, does not exhibit EDRF-inhibitory properties.

All of these results showing the ability of hemoglobin to block EDRF/NO-induced relaxation point to an interaction between the two in the pathogenesis of vasospasm.

Free radicals and vasospasm

There is evidence to suggest that free radical formation after subarachnoid hemorrhage may contribute to the development of vasospasm. The TBA test utilizes thiobarbituric acid (TBA) to detect the presence of malondialdehyde (MDA), a product of free radical reactions. Sasaki used this test to detect increased amounts of lipid peroxides in CSF and arterial walls in dogs after experimental subarachnoid hemorrhage(236). Other studies have shown a correlation between the severity of spasm and CSF levels of MDA in animals(168). Several studies in humans of CSF levels of TBA-reactive compounds have also demonstrated a correlation between spasm and increased lipid peroxide levels(235, 238).

However, intrathecal administration of free radicals has not been conclusively shown to produce vasospasm mimicking that observed after subarachnoid hemorrhage. Moreover, in the studies that have shown some degree of arterial constriction associated with the presence of free radicals, the characteristic pathological changes of cerebral vasospasm are absent(32, 290).

It has been proposed that the reason that OxyHb, but not MetHb, is a key contributor to vasospasm is that when OxyHb is oxidized, it releases superoxide anion (O_2^-). Superoxide then theoretically interacts with and inactivates NO, leading to vasospasm. However, conflicting papers exist as to the veracity of this

theory. While Kamiyama and others have published observations that superoxide dismutase, which scavenges superoxide, lessens the inactivation of NO by OxyHb(135, 257), Fujita and other authors have published negative results using this enzyme(82, 169).

One promising compound, U74006F (Tirilazad), has been shown in both primate and human studies to lessen angiographic vasospasm when used prophylactically. Still in clinical trials, this 21-aminosteroid has potent free radical-scavenging properties and inhibits iron-dependent lipid peroxidation(97, 173).

Management strategies for vasospasm

Timing of aneurysm surgery

Much has been published regarding the issue of early surgery and the incidence of vasospasm. Certainly early surgical clipping of a ruptured aneurysm allows for more aggressive management of any complications, including vasospasm, because the risk of rebleeding has been effectively eliminated. In the past, though, it was believed that managing the patient conservatively through the period of maximal risk of vasospasm allowed for a better surgical outcome later. Many studies from the 1950's to 1970's supported this(92, 192, 220). The philosophy of early surgery has only recently supplanted this. Early results were skewed due to the high mortality among high-risk patients undergoing early surgery.

The largest trial comparing the two philosophies was the nonrandomized, prospective International Cooperative Study on Timing of Aneurysm Surgery (CASTOS)(139). Those patients assigned to undergo surgery between days 4 and

10 after aneurysmal rupture developed ischemic deficits from vasospasm most often. Deficits were most likely to appear during this period and many of these patients probably had their operation deferred due to vasospasm. Symptomatic spasm was least common in those undergoing surgery within 3 days of hemorrhage(141).

Other studies have shown a clear advantage to early surgery in reducing spasm. Suzuki and colleagues' 1979 study showed that patients operated within 48 hours had a mortality rate of less than 12% while operation between days 3 and 5 led to a rate of over 20%(269). Chyatte, *et al.* reported results from a retrospective study that patients benefited from early operation even though their cohort tended to be of lower clinical grades and exhibit more ischemic symptoms prior to surgery(41). In the prospective trial conducted by Solomon, *et al.*, early surgery was associated with a 16% incidence of symptomatic vasospasm, versus 28% in those patients operated on between days 4 and 7(252).

A randomized trial involving 216 patients conducted by Öhman and Heiskanen could find no difference in the incidence of spasm-related deficits between groups of patients assigned to early and late surgery (25% vs. 24%, respectively)(198). Moreover, Macdonald's group conducted angiographic measurements of the ICA, ACA and MCA at 8 different points in 56 patients(166). They also found no disadvantage to early surgery in terms of the incidence of spasm. These results have led to the increasing adoption of early surgery as the standard of care in all but the worst grade patients who are to unstable to withstand surgery.

Subarachnoid clot removal at surgery

Given that the most significant predictor of vasospasm is the amount of subarachnoid blood visible on CT scan and the evidence supporting hemoglobin as a spasmogen, aggressive clot removal has been investigated as a way of preventing spasm.

Primate studies carried out by Nosko and colleagues helped to establish the efficacy of this strategy(196). Animals were divided into 3 groups - those selected for sham surgery, those receiving placement of autologous clot around the circle of Willis, and those receiving clot placement and subsequent clot removal within 24 hours. The entire cohort who did not have clot evacuation developed spasm. Both of the other groups (sham surgery and clot with removal) were free of any spasm. Further studies by Handa demonstrated the progressive severity of vasospasm at 48-, 72- and 96-hour intervals following experimental clot placement(100).

Taneda's retrospective work demonstrated that extensive clot evacuation during early surgery (within 48 hours) cut the incidence of spasm in half, as compared to patients just undergoing early surgery(271). Many of the infarcts that did develop were contralateral to the operative side. This led him to theorize that more clot remained on the non-operative side, thus increasing the risk of spasm. In the early 1980's, Mizukami, *et al.*, reported that clot removal from around an artery totally prevented angiographic spasm in that vessel after early surgery(184).

Hypertensive hypervolemic therapy

Since the earliest report by Denny-Brown in the 1950's(55), it has been repeatedly documented that intravascular volume expansion and hemodilution with or without induced hypertension leads to an improvement in neurological deficits from vasospasm and in overall outcome.

This benefit stems from the therapy's effect along several fronts. Expanding the intravascular volume improves cardiac output via movement along the Frank-Starling curve, thereby improving the delivery of blood through the spastic vasculature. Colloid infusion serves also to correct the hypovolemia present in many patients with subarachnoid hemorrhage. In addition, the concomitant lowering of the hematocrit improves the rheology of the blood by lowering viscosity. Moreover, it has been demonstrated in many human and animal studies that cerebral autoregulation is disrupted after subarachnoid hemorrhage(99, 104, 106). This leaves the cerebral perfusion pressure dependent upon the systolic arterial pressure. Therefore, increasing systolic pressure may directly increase cerebral perfusion pressure and modest drops in pressure are poorly tolerated by the patient.

The general protocol involves the infusion of crystalloid or colloid (albumin, hetastarch, etc.) to achieve a central venous pressure (CVP) of between 8 and 12 mmHg and a pulmonary capillary wedge pressure (PCWP) of between 10 and 18 mmHg. Invasive monitoring by central venous or Swan-Ganz catheter is uniformly conducted. In patients with an unclipped aneurysm, care is taken not to raise the systolic blood pressure above 150-160 mmHg. However, once the aneurysm is secured, pressors such as dopamine, dobutamine, or isoproterenol may be employed to increase the pressure as high as 200 mmHg as required. As more clinical data has become available, it has become more common to adjust

the blood pressure, CVP, PCWP, and cardiac output in each patient according to the neurological exam. The "optimal" therapy is that which results in a stabilization or resolution of those ischemic deficits attributable to cerebral vasospasm.

The benefits of this therapy have been repeatedly borne out in clinical trials. The series of 58 patients reported by Kassell, *et al.* in 1982 demonstrated reversal of neurologic deficits in 74% (43/58) of patients placed on a regimen of volume expansion and pressors(137). Awad and colleagues studied 118 consecutive patients admitted over 2 years who were treated with a uniform protocol of early surgery, volume expansion, and hypertension in post surgical patients (as required)(12). Forty-two patients (35.6%) developed clinical spasm. After hemodynamic therapy, 60% had improved by at least one clinical grade (Hunt/Hess). Almost 81% of patients were discharged with either no or minor deficits.

A large meta-analysis by Dorsch of 31 reports of pre-operative hypervolemic therapy found an incidence of clinical vasospasm of only 17.6%(58). Combining 73 reports listing the outcome of 2111 patients who had received fluid loading, he found that 54% of patients went on to a "good" outcome (able to resume normal activities). Permanent deficits were present in 28.5% of patients and 17.5% died.

This treatment is not without risks. A study of intracranial complications of hypervolemic therapy by Shimoda, *et al.*, found that 19% of patients experienced aggravation of cerebral edema and 9% developed hemorrhagic infarcts(249). The increased edema is thought to be the result of impairment of the blood brain barrier after subarachnoid hemorrhage. Hypertension without volume expansion (normovolemic) was introduced by Otsubo's group in an effort to avoid the pulmonary edema that may accompany increases in the

PCWP(208). Just over half (54%) of their 41 patients improved, with only one case of pulmonary edema reported. However, one-fifth of the patients in their study went on to develop hemorrhagic infarcts, presumably as a result of the hypertension. Other risks include complications from line insertion (infection, pneumothorax, hemothorax), cardiac failure due to fluid overload, and rerupture of unsecured aneurysms.

Calcium Channel Antagonists

As stated earlier, arterial smooth muscle contraction is mediated by calcium binding to calmodulin (CaM) and the subsequent activation of myosin light chain kinase by the Ca-CaM complex. Phosphorylation of myosin allows it to bind actin and cause contraction. Theoretically then, blocking the influx of calcium into the intracellular space should prevent arterial spasm. Calcium channel antagonists are now routinely used in patients with subarachnoid hemorrhage, the most common being the cerebroselective dihydropyridine nimodipine. Nicardipine, another compound in the same class has also been studied. However, the magnitude of their utility is somewhat controversial.

The ability for calcium channel blockers to vasodilate cerebral arteries is still somewhat in dispute. Vinall and Simeone demonstrated that nimodipine was able to dilate bovine cerebral vessels when applied both intraluminally and extraluminally(293). On the other hand, a trial of nimodipine in a primate model of subarachnoid hemorrhage by Espinoza, *et al.*, demonstrated no angiographic improvement in spasm after 7 days(67). Other studies published by Nosko, *et al.*, and Krueger, *et al.* have also failed to show angiographic resolution with nimodipine administration(151, 196). In one trial, Auer reported a positive outcome in 77% of patients treated with nimodipine but observed no

angiographic effect on vessels with a diameter greater than 70 μ m, leading to speculation that the compound may exert its effect at the level of the pial vasculature(11).

The first results of a large randomized prospective study of calcium antagonists in subarachnoid hemorrhage were published in 1983 by Allen and colleagues(7). They enrolled good grade (Hunt and Hess I and II) patients within 96 hours of the hemorrhage. Only 1.7% of the patients receiving nimodipine died or were left with a severe deficit, as opposed to 13.3% of the patients in the placebo group.

Petruk, *et al.*, randomly treated 154 poor grade (Hunt and Hess III, IV and V) patients with nimodipine or placebo(214). Treated patients were 3 times as likely to have a good recovery (Glasgow Outcome Scale 1-2), even though there was no difference in the incidence of moderate or severe diffuse angiographic spasm. This finding was confirmed in one of the largest randomized trials to date, the 1989 British Aneurysm Nimodipine Trial (BRANT)(217). In that report, Pickard and colleagues studied 544 patients and found nimodipine significantly reduced the incidence of infarction and poor outcome at 3 months. Once again, though, there was no significant difference between drug and placebo groups in the incidence of vasospasm on angiography. Philippon, *et al.*, also reported that while patients treated with nimodipine had fewer poor outcomes due to spasm, there was no difference in angiographic evidence of spasm(215). Säeveland's group has also published similar findings(229).

In contrast to these studies, several reports have emerged showing that despite a lower incidence of spasm, treatment with calcium antagonists does not affect outcome. Mercier, *et al.*, compared patients treated with vascular expansion and calcium channel blockers with historical controls(179). They found no significant improvement in neuropsychological testing and return to

work 2 months after discharge. These findings are in accordance with an earlier series by Pellettieri, *et al*(210).

In general, while these and other papers report no advantage to using calcium antagonists, it appears that nimodipine does have a beneficial effect on outcome. Dorsch combined 14 references reporting patient outcomes and found the common odds ratio for a poor outcome (death and permanent deficit) to be 1.68 (95%CI 1.40-2.01) without calcium channel blockers(58).

Calcium, however, may enter the cell via a number of routes. Both ligand- and voltage-sensitive membrane channels exist. Moreover, there are intracellular stores in organelles such as the endoplasmic reticulum. Since current calcium antagonists are only effective at blocking influx through voltage-sensitive channels, the role of calcium and calcium channel blockers in vasospasm must be more complex. In addition, since the incidence of angiographic spasm is frequently not reduced by nimodipine, these compounds must also act via some other mechanism.

As stated above, one thought is that their primary site of action is on the smaller pial vessels. Another theory is that nimodipine exerts a protective effect on neurons made ischemic by spasm. By blocking the neurotoxic calcium influx associated with ischemic cell death, calcium channel antagonists may prevent infarction and improve outcome(180). However, the full body of evidence needed to support this theory is still being gathered.

Transluminal angioplasty

Zubkov, *et al.* were the first to use balloon dilatation of the cerebral vasculature as a treatment for vasospasm after subarachnoid hemorrhage(310).

Unlike nimodipine, which is primarily a prophylactic agent, angioplasty promises to reverse neurological decline after the onset of cerebral vasospasm.

While a vast amount of literature regarding this therapy is not available, the reports published so far are promising. In earlier reports, it was mainly used when hemodynamic or pharmacologic treatments had failed. Dorch's meta-analysis of 13 reports detailing patient outcome reveals favorable results in 53% of patients with 20% dead and 27% with permanent deficits(58). Complications, such as the rupture of a vessel during balloon inflation or the production of a hemorrhagic infarct due to reperfusion of an ischemic region, have been rare(66, 89, 148, 158).

Since neurological deficits are most easily reversed when treated early, consideration is now being given to the selection of patients for early application of angioplasty. Most reports state that angioplasty is most effective when performed early in the course of vasospasm, before angiopathic changes such as fibrosis have occurred(16, 34, 50, 66, 81, 111, 112, 118).

Unfortunately, this procedure is not curative. Patients have been reported to suffer recurrent spasm after balloon dilatation(66, 309). Moreover, even with superselective catheterization, only the larger vessels of the circle of Willis and the most proximal branches may be treated. This leaves the medium sized vessels, the perforating vessels, and the distal vasculature unaffected.

Intraarterial papaverine

Intraarterial infusion of papaverine hydrochloride has been tried in an attempt to dilate as much of the cerebral vasculature of possible. Papaverine is believed to exert its vasodilatory effect through inhibition of phosphodiesterase, thereby increasing the intracellular levels of cyclic adenosine monophosphate

(cAMP). The drug is usually administered via selective or superselective catheterization during cerebral angiography(134, 176, 286).

Several series have demonstrated resolution of angiographic spasm after papaverine infusion with improvement in neurological deficits. Clouston, *et al.* reported 50% (7/14) patients with marked clinical improvement within 24 hours of infusion(43). However, only 1 of these patients experienced complete resolution of neurological deficits.

The major drawback of the therapy is the short half life of papaverine. Many patients require multiple treatments and some appear to have spasm refractory to papaverine treatment. Currently there is no method for distinguishing which patients will benefit. In addition, angiographic improvement of spasm after papaverine infusion does not appear to always correlate with clinical improvement. Sequential angiograms for repeating treatment expose the patient to further risks. Moreover, many patients with severe spasm are too unstable to undergo the procedure. So far, it appears that papaverine remains an adjunctive therapy for, but not a solution to, cerebral vasospasm(287).

Tissue-type plasminogen activator

The success of intraoperative subarachnoid clot removal at reducing the incidence of cerebral vasospasm after subarachnoid hemorrhage has sparked interest in the use of tissue-type plasminogen activator (tPA) to lyse the clot preoperatively. As opposed to urokinase, tPA is specific for fibrin-bound plasmin and causes less systemic fibrinolysis.

Findlay's early studies demonstrated that 11 of 12 animals receiving intracisternal tPA injections were free of any subarachnoid clot, while all of the

control animals still had thick clot present(73). This corresponded to a lesser degree of spasm in the treatment group. Other work by his group and others has helped to document that tPA is most useful if administered within 48 hours after subarachnoid hemorrhage(71, 72, 145). A preliminary study by Mizoi, *et al.* demonstrated the complete prevention of spasm in a group of 10 patients admitted with Fisher grade 3 hemorrhage on CT scan(182).

A prospective study performed by the same group examined 30 patients who received postoperative intracisternal tPA infusions(183). Compared to the 75 control patients, the treatment group had more severe subarachnoid blood on CT scan at admission (greater than 75 Hounsfield units versus less than 75HU), but no cases of delayed ischemic deficits, as opposed to 11 cases (15%) among controls. Seifert and colleagues have documented similar results in a recent trial involving 52 tPA patients and 68 controls(243). In a 1994 report, Steinberg, *et al.* published the apparent failure of tPA to prevent spasm in 4 of 8 treated individuals(261). They believe this may relate to inadequate clearing of the subarachnoid clot, pre-existing poor collateral supply, or the occurrence of prior subarachnoid hemorrhage. Hariton has published tPA's failure in a dog model of subarachnoid hemorrhage(103).

Complications have been few. Several cases of subarachnoid hemorrhage due to mechanical trauma during catheter removal have been reported. Epidural hematoma and local bleeding may also occur(72, 73, 182, 183, 237, 241). While this appears promising, further studies are still necessary to fully document its efficacy.

Tirilazad mesylate

As previously mentioned, tirilazad is a 21-aminosteroid shown to inhibit iron-dependent lipid peroxidation and to scavenge free radicals. There has been some experience in monkey, rabbit, and dog hemorrhage models that demonstrates the ability of tirilazad to reduce the production of vasoconstrictive prostaglandins and enhance the synthesis of prostacyclin(85, 173, 262, 295). A phase II trial conducted at 12 Canadian centers has established the safety of the drug and clinical trials are continuing(97). Preliminary results presented show a benefit in men and trials are underway to determine the benefit to women.

Other investigational therapies

Building on evidence that the chronic phase of vasospasm may be partially the result of an inflammatory vasculopathy, trials of anti-inflammatory agents have been conducted. Chyatte's work has focused on using ibuprofen or methylprednisolone and has shown some promise in canine models(39). In addition, a trial of tapering doses of methylprednisolone in 21 patients demonstrated a reduced incidence of delayed ischemic deficits and significantly better overall outcomes as compared to 21 matched historical controls(40).

Immunosuppressive agents have also been tested. Peterson, *et al.* reported a reduction of 42% in vasospasm as measured by angiography in dogs treated with cyclosporine A and dexamethasone (80% vs. 65% of baseline diameter)(212). Ryba's group administered 2-chlorodeoxyadenosine to 20 patients after subarachnoid hemorrhage(227). In 80% of patients, a good outcome was achieved. Only 1 patient was left with a severe deficit.

Summary

Cerebral vasospasm following aneurysmal rupture is the major cause of morbidity in patients surviving the initial hemorrhage. Almost one third of patients will develop delayed ischemic neurological deficits due to vasospasm. Treatment with early surgery, hypervolemic therapy and calcium channel blockers helps to decrease the incidence by about half. However, in spite of these treatments and other investigational therapies, vasospasm still poses a significant threat in patients with subarachnoid hemorrhage. Further efforts are required to develop a truly adequate therapy.

Chapter 3: Vascular Effects of Estrogen

In recent years, it has been demonstrated that premenopausal women are at a significantly lower risk for cardiovascular mortality than are men. However, the observation that this difference fades soon after women undergo menopause has led researchers to hypothesize that estrogen may be the beneficial agent. It appears that postmenopausal women taking hormone replacement experience a reduction of approximately 33% to 50% in the incidence cardiac events. Moreover, the incidence of cerebrovascular events is also decreased by half in this population(30, 256). Further studies have documented profound vascular effects of estrogen and justify the investigation of its effects on cerebral vasospasm.

Estrogen and the vascular endothelium

A number of reports have emerged detailing estrogen's capacity to cause vasodilatation. The primary estrogen in humans, 17 β -estradiol, has been shown to dilate the several arterial beds, the most widely studied being those of the uterus and vagina. In pigs, the highest uterine blood flow is observed during estrus, the time when estrogen levels are at their peak(79). Increased blood flow is observed approximately 20-30 minutes after the administration of exogenous estrogen. This delay is less than that expected of a steroid hormone acting through the usual genomic mechanisms. This has led researchers to theorize that estrogen is acting via the rapid production or release of a local mediator.

Shamma, *et al.* observed that middle cerebral artery blood flow velocity in women undergoing ovarian hyperstimulation was greatest at the time of peak estrogen levels(246). A report by Brass found a similar association between cerebral blood flow velocity and estrogen levels during the menstrual cycle(27). In addition, Bartelink found skin blood flow in women to be at its lowest during menstruation, the time of lowest estrogen concentrations(18).

A growing number of reports indicate that this local mediator of spasm may be nitric oxide. The ability of estrogen treatment to augment acetylcholine-induced endothelium-dependent vasodilatation in the coronary circulation has been well documented(65, 109).(90, 303) Atherosclerosis causes acetylcholine (ACh) to vasoconstrict instead of vasodilate, possibly due to damage to the endothelium and the loss of endothelium-dependent vasodilatation. Williams, *et al.* showed that oral estrogen given to oophorectomized monkeys with induced coronary atherosclerosis restored the normal response to ACh(304). In another paper, the same group obtained similar results using subcutaneous administration(303). However, the effect of the oral preparation was less than that achieved with parenteral estrogen (dilation of 11% versus 21% to 35%). They also found that the addition of a progestin significantly blunted the vasodilatory effect of the estrogen. The coronary and femoral circulations of the rabbit has been proven to be similarly affected(48, 91).

Collins and colleagues studied the effect of intracoronary estradiol on the response to ACh in postmenopausal women and age-matched men(47). In the women, the response of coronary flow to ACh improved from a 126% to a 248% increase after estradiol pretreatment. As in the animal studies, in some subjects ACh caused vasoconstriction prior to estradiol and vasodilation afterwards. The onset of the enhancement was within 30 minutes of estradiol infusion. The male subjects showed no vasodilation in response to ACh after estradiol.

Gilligan, *et al.* utilized a strain gauge to study the change in the ACh response in the forearm circulation after intraarterial estradiol administration(90). Estradiol increased ACh's effect by 18% in those women with risk factors for "endothelial dysfunction" (coronary artery disease, hypertension, hypercholesterolemia, or diabetes mellitus). The increase was 14% in those women without risk factors.

Estradiol has been shown experimentally to directly interact with the nitric oxide system. Nitric oxide release from female rabbit aortic rings is increased by estradiol as long as the endothelium is intact(48). Moreover, estrogen stimulates the production of NO by cultured bovine endothelial cells(33). Van Buren, *et al.* found that L-nitroarginine methyl ester (L-NAME), an inhibitor of NO-synthetase, blocks estrogen's effects on the uterine vasculature(283). Also, increased serum levels of estradiol have been associated with lower levels of the endothelium-derived vasoconstrictor endothelin(219).

These data indicate that estrogen may cause vasodilatation through a rapid, non-genomic mechanism that appears to interact with, and stimulate, the NO system. Through this action, estrogen may have utility in cerebral vasospasm after subarachnoid hemorrhage, given the evidence presented earlier that spasm may be due in part to the impairment of NO release or its binding by OxyHb.

Estrogen as a calcium channel blocker

Aside from its effects on endothelium-dependent vascular relaxation, estrogen appears to also possess direct vasodilatory capacity independent of the endothelium. Several groups, including Jiang. *et al.* have found that L-NAME does not always block the vasodilatory response to estrogen *in vitro*(127, 267). Moreover, inhibiting guanylate cyclase with methylene blue also does not always

affect estrogen-induced relaxation(127). The addition of reduced hemoglobin in their experiments also did not abolish the effect(127). However, when investigating the influence of the concentration of extracellular calcium, the investigators found that the curve was significantly shifted to the right, indicating that estrogen may be acting via the inhibition of calcium entry into the myocytes(126, 128).

Stice, *et al.* were the first to report the estrogen's inhibition of calcium-induced contraction of arterial smooth muscle(266). They noted that treatment with 4-hydroxy estradiol (4-OH-E₂), a major metabolite, decreased the baseline perfusion pressure and doubled vessel diameter in an *in vitro* setup of porcine uterine arteries. Moreover, the vessel responsiveness to increasing levels of extracellular calcium was decreased. In another study, this group noted that the uptake of calcium by uterine arteries decreased in the presence of high estrogen levels(265).

While this effect is postulated to involve potential-sensitive calcium channels, estradiol has been shown to augment contraction via receptor-operated calcium channels. These channels are linked to α_1 -adrenoceptors that are sensitive to norepinephrine. Papers by the groups led by Bento and Cheng have documented a heightened sensitivity of the rat aorta to norepinephrine after treatment with estrogen(21, 37, 265). They concluded that this is due to an increase in the number of these adrenoceptors. Gisclard, *et al.*, however, studied the rabbit femoral artery and reported a decrease in the norepinephrine contractile response after estrogen treatment(91). From these conflicting results, it may be assumed that while estrogen has some influence on the movement of calcium across the vascular wall, the nature and magnitude of that effect must still be further defined.

Vasospastic conditions and estrogen

Syndrome X

Syndrome X consists of chest pain typical of myocardial ischemia associated with a positive exercise stress test and a coronary angiogram that fails to document any vascular lesions. The chest pain is not always exercise-induced and the response to nitrates varies. Some patients may suffer numerous myocardial infarctions. The disorder is more commonly found in women(122, 233, 234).

One consistent finding among these patients seems to be a decreased vasodilatory capacity. Chauhan, *et al.* demonstrated that asymptomatic women display a significantly greater increase in coronary blood flow in response to the intracoronary infusion of papaverine or acetylcholine(36). Egashira's group and Holdright, *et al.* have produced similar results(64, 116).

Sarrel and colleagues have reported that women with syndrome X frequently have evidence of estrogen deficiency(234). In their series of 30 women, all had serum estradiol levels of <25 pg/mL (normal >50 pg/mL) at the time of chest pain. Moreover, 25 of the women experienced greater than 20 hot flushes per day, frequently accompanied by chest pain. Interestingly, the forearm vasodilator reserve was decreased in these women as compared to controls. Treatment with transdermal estradiol for several weeks significantly alleviated symptoms and increased the forearm vasodilatory response.

Raynaud's phenomenon and menstrual migraine

Raynaud's phenomenon is a vasospastic condition of the digital vasculature usually induced by exposure to cold temperatures. The fingers of affected patients turn gray or white and may feel numb. Another disorder attributed to vasospasm is menstrual (or catamenial) migraine, in which headaches occur regularly at specific times during the menstrual cycle. They are usually preceded by an aura and are relatively refractory to most pharmacologic therapies. These disorders are frequently found in the same patients and an increasing body of evidence suggests that insufficient levels of estrogen may be at work.

In the study by Sarrel mentioned above, 43% of the women reported suffering from migraine headaches. Zahavi, *et al.* reported a 26% incidence of Raynaud's phenomenon among 111 women with migraines, as opposed to only 6% of controls(308). Leppert's group has also found a significant association between these conditions(155). There is clinical evidence that the administration of estradiol during a migraine may blunt or even totally abort some women's migraines(27, 299). It is a growing practice for these women to take estradiol supplements during the period they usually experience headaches. Serum estradiol measured at the time of an attack usually shows a level below 50 pg/mL.

These clinical correlates, along with the experimental results presented above, provide strong evidence for a vasoactive role for estrogen. It is hoped that this property can be utilized to favorably modify the course of cerebral vasospasm.

Chapter 4: Transcranial Doppler Ultrasonography

The noninvasive measurement of the blood flow velocities in the intracranial circulation was first reported by Aaslid in 1982(3). While ultrasonography had been used to study the extracranial circulation for more than 2 decades, the skull had always posed a challenge to the development of a comparable intracranial technique.

Principles and techniques

The Doppler principle

The Doppler principle describes the alteration in the frequency of a wave reflected by a moving object. According to this law, the frequency of the wave will be increased if the object is moving towards the observer. Conversely, an observer will detect a lower reflected frequency if the object is receding.

The ultrasound transducer functions as both emitter and receiver of the ultrasonic wave. The wave is reflected off moving erythrocytes within the vasculature. The altered frequency received by the transducer allows for the calculation of the speed of the erythrocytes.

$$\text{Freq Shift (MHz)} = \frac{2 \cdot \text{flow velocity (m/sec)} \cdot \text{emitted freq (MHz)} \cdot \cos \Theta}{\text{speed of wave (m/sec)}}$$

The greatest value (that closest to the true velocity) will be achieved when the angle of insonation (Θ) is 0° . Direction is determined in addition to the speed, giving a true measurement of velocity, a vector quantity. The mean and peak flow velocities are monitored as well as a pulsatility index (PI), calculated as $V_{\text{systolic}} - V_{\text{diastolic}} / V_{\text{mean}}$. The PI does not depend on the angle of insonation and normally ranges between 0.5 and 1.1(157, 274). It is used to describe how bounding a velocity wave is. For example, in a patient with severe carotid artery disease, the atherosclerotic artery damps the usual variations in flow velocity, resulting in a low pulsatility index.

Transcranial Doppler ultrasound (TCD)

Transcranial Doppler ultrasound (TCD) utilizes a probe (usually hand-held) emitting a sound wave at 2 MHz. This is a lower frequency than the 5 to 10 MHz devices used for studying the cervical carotid artery and other systemic vessels. The skull causes less signal attenuation at the lower frequency, much like the walls of a house allow bass sound to pass through easily. Monitoring is performed through so-called "windows", areas of the skull that are thin enough to allow penetration of the ultrasonic wave. The most common are the temporal window, located just above the zygoma; the suboccipital window, located at the foramen magnum; and the orbital window, actually the orbit itself. The temporal window allows access to the intracranial ICA, the MCA, the ACA, and the PCA. The orbital window provides for monitoring of the ICA and ophthalmic artery. The posterior circulation is studied via the foramen magnum(3, 157, 190, 239, 274).

TCD samples the circulation in 5mm steps. The specific vessels are best identified by the depth of sampling and the direction of flow observed. Since the

temporal window was used in the studies in this thesis, all values relate to those observed via that location. The MCA is usually found at depths between 35mm and 60mm with blood flowing towards the transducer. Normal peak velocity is between 85 and 100 cm/sec with a mean velocity of 40 to 65 cm/sec. The ACA may be insonated between 65mm and 75mm and is characterized with blood flow away from the transducer. Typical values from 70 to 80 cm/sec peak and 65 to 75 cm/sec mean. The ICA is usually found at approximately 60mm to 65mm and may exhibit bidirectional flow if the bifurcation is insonated(56, 190).

Blood flow velocity versus blood flow

The data produced by TCD do not provide direct information as to the amount of blood reaching the brain. The blood flow through a vessel is related to the velocity of the blood (V) and the cross-sectional area of the vessel (A), or $Q=V*A$. Theoretically, for the cerebral blood flow (CBF) to remain constant during spasm (a decrease in A), the flow velocity must increase. However, the plot of velocity versus lumen diameter is not a direct relationship. As the diameter begins to decrease, flow velocity rises. However, as the stenosis becomes greater, velocities actually decrease as flow is choked off.

Sorteberg and colleagues conducted a study to relate regional CBF and TCD values(255). Even though they did find positive correlations, their study design is hampered by the fact that the CBF and TCD studies were not performed together. Sekhar, *et al.* reported a general relationship between increased TCD velocities and decreased CBF, but no firm correlation could be determined(245). Other studies have also been unable to establish results more definite than these in a clinical setting.

In addition, factors such as intracranial pressure, hematocrit, blood pressure and P_{CO_2} , have all been proven to affect TCD results(153, 157, 190, 207). There have also been no studies documenting any effect of current treatments for spasm, such as nimodipine and hypervolemia, on CBF and TCD velocities.

TCD in subarachnoid hemorrhage

TCD ultrasound has become an increasingly useful tool for the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. It is a relatively inexpensive , noninvasive bedside procedure that may be repeated as often as needed. TCD may be used not only for the diagnosis of spasm, but also to judge its severity and monitor the clinical course.

Flow velocity measurements during vasospasm

Most investigators have found that the time course of the flow velocity increase observed during spasm parallels the course described earlier for the angiographic appearance of spasm. In general, velocities begin to increase after the first 2 days since the hemorrhage. They continue to escalate into the second week and may remain elevated for several days before beginning to fall(2, 102, 157, 190, 263).

There are no uniform criteria that would allow the establishment of a definite velocity criterion for the diagnosis of vasospasm since rheologic properties that affect velocity, such as hematocrit and blood viscosity, are manipulated in spasm. In a 1984 paper, Aaslid, *et al.* set a mean velocity of 120 cm/sec as vasospastic on the basis of their correlation of velocities greater than this with the presence of angiographic spasm(1). This level has generally been

accepted in most centers, with some adopting a higher cutoff of 150 cm/sec, depending on clinicians' experiences. Lindegaard's calculations taking into account a normal speed of 62 cm/sec, a 50% decrease in vessel diameter, and a 40% reduction in cerebral perfusion result in a velocity of 150 cm/sec(157).

Aaslid and Lindegaard have become the biggest proponents of using the ratio of the velocity in the MCA to that in the extracranial ICA for diagnosing spasm. They argue that using the ICA as a comparison corrects for such measures as hypervolemic therapy and pressors that could raise the flow velocity in the intracranial vessels without representing spasm. A ratio of 3 is indicative of moderate spasm while a value of 6 shows severe spasm(2, 157). In one of Lindegaard's studies, the agreement between the ratio and angiographers' opinions was significant ($\kappa = 0.72$)(156).

Harders and Gilsbach performed serial TCD exams on 50 patients during hospitalization and then during the ensuing several months after discharge(102). In the 29 patients admitted with Hunt/Hess grade III subarachnoid hemorrhage, velocities began to rise on day 3 post-bleed and appeared to plateau between days 7 and 15. A return to normal began around day 19 and were near baseline again about a month after the hemorrhage. The greatest changes were observed in the MCA and ICA on the operative side.

Two aspects of cerebrovascular anatomy make it difficult for TCD velocities to truly reflect vasospasm(157, 190, 207, 239, 250). Unfortunately, TCD can only evaluate the larger vessels of the circle of Willis, and not the smaller vessels that are also involved in spasm. Vessels beyond the M₁ and A₁ segments are not reliably insonated. As a result, velocities in the monitored vessels may appear only slightly increased while the resistance vessels are in spasm. Collateral flow also hampers the accuracy of TCD. For instance, spasm of the ipsilateral A₁ may be masked by collateral flow through the anterior

communicating artery. In some cases, reversal of flow in the ACA may be observed, allowing one to assume spasm is present. However, at times this is highly dependent on the technician and the angle of insonation. Aaslid and others have established that flow velocities in the MCA are more reliable, due to the lack of significant collateralization(1, 2, 250).

Prediction of delayed ischemic deficits

Ultimately, the utility of TCD lies in its ability to predict which patients are at risk for the development of delayed ischemic deficits from cerebral vasospasm. A number of studies have been conducted to test the validity of TCD. Among 6 studies that focused on the MCA in a total of 274 patients, the sensitivity ranged from 68% to 94% with a positive predictive value of between 57% to 95%. The specificity was better, between 89% and 100%. However, the diagnostic velocities varied from 100 cm/sec (1 study) to 120 cm/sec (2 reports), to 150 cm/sec (1 paper)(250).

A number of investigators have published reports that show a sharp increase in mean flow velocities 24 to 48 hours before the onset of neurological symptoms from vasospasm. Laumer, *et al.* found that patients with grade 2 subarachnoid hemorrhage on CT according to the Fisher scale had significantly greater mean MCA velocities than those diagnosed as grade 1(153). However, there was no difference between the grade 2 and grade 3 patients. Among their 66 patients, 8 remained asymptomatic with mean velocities over 200 cm/sec. Another 16 suffered symptomatic spasm without elevated TCD flow velocities. Most patients who developed deficits did not display an increase in flow velocity just before their onset.

Davis' group had more optimistic results(54). While half of their asymptomatic patients had TCD evidence of spasm, 16 of 18 who developed deficits had correlating TCD exams. Moreover, in those patients with a lateralized deficit, SPECT studies showed a significant concordance with TCD results and clinical course. Sekhar, *et al.* have also found TCD to be useful in predicting spasm(245). Between days 4 and 12 post-hemorrhage, patients that developed spasm had significantly higher MCA and ACA velocities bilaterally than those that remained asymptomatic. Mean velocities in the spasm group were 168.9 cm/sec on average, as opposed to only 97.6 in the group without spasm.

In conclusion, TCD is a useful method for detecting and monitoring the course of cerebral vasospasm following subarachnoid hemorrhage. However, it is highly operator dependent and does have several technical limitations. It detects spasm in the MCA with the greatest accuracy but it is not as reliable with respect to other vessels and cannot directly assess the smaller resistance vessels. However, when correlated with clinical observations, TCD is a valuable adjunct to the therapies described earlier.

Chapter 5: Methodology of Prospective Pilot Study of Effect of Estrogen on Vasospasm

Patient selection

Women aged 18 years and older who had suffered a aneurysmal SAH were eligible for enrollment in the study. Over 50 women were screened for inclusion during 1995 by the author. Estradiol, follicular stimulating hormone (FSH) and progesterone levels (all monoclonal autoimmune antibody assay) were measured at the time of enrollment in the study and were followed daily. Exclusion criteria included standard contraindications to estrogen therapy, such as a history of endometrial cancer, thrombotic episodes (such as deep venous thrombosis), porphyria or current pregnancy. A total of 9 women were enrolled. The women ranged in age from 25 to 77 years of age (mean 50 years). Three of the women developed vasospasm and entered the treatment phase of the study.

Study procedures

All patients underwent cerebral angiography to identify the source of the hemorrhage and early operation for clipping of the ruptured aneurysm. All patients received nimodipine and dilantin prophylactically. Hypervolemia and induced hypertension were utilized only if symptomatic spasm was present and not simply for elevated TCD velocities.

All patients were monitored daily for the development for vasospasm with serial TCD studies using a standard 2MHz hand-held probe (Medasonics CDS system, Medasonics, Fremont, CA). The basic aspects of TCD examination

have been described elsewhere in detail. Insonation was performed through the temporal window bilaterally at depths ranging from 45 to 75mm in 5mm increments. The peak and mean blood velocities were recorded, along with the pulsatility index.

Estradiol (Estrace[®], Bristol-Myers Squibb Company, Princeton, NJ), 1mg sublingually, was administered only if patients developed vasospasm, defined as a mean blood velocity on TCD examination exceeding 120 cm/sec in one or both middle cerebral, anterior cerebral, or internal carotid arteries. The blood velocity in the spastic segment was followed for 20 minutes prior to the administration of estradiol to establish a stable baseline. Monitoring continued for 120 minutes post-administration (every 5 minutes until 40 minutes after administration of estradiol and then every 20 minutes thereafter). All data was entered into a Helix Express[®] database constructed by the author. Results were analyzed using a paired t-test comparing the mean value during the immediate pre-treatment (baseline) period to the value obtained at each monitoring time point. Microsoft Excel[®] was used for the analysis of data and Cricket Graph[®] for graph construction.

Patients were screened and enrolled by the author after identification by Drs. Awad and Dickey. All data collection, including most TCD ultrasound exams and all estradiol treatment, was conducted by the author. All data analysis was performed by the author.

Symptomatic Patient Profiles:

Patient 1: This 28 year-old right-handed woman presented one evening after experiencing the onset of the worst headache of her life while watching television. She became nauseated and vomited.

Upon presentation to the emergency room, she was oriented but lethargic. She was photophobic and exhibited mild nuchal rigidity (Hunt/Hess grade 1). Her neurological exam was nonfocal. A CT scan revealed a Fisher grade 1 SAH.

She underwent clipping of a right posterior communicating artery aneurysm approximately 36 hours after the onset of her hemorrhage. Her estradiol level on admission was <15 pg/mL and she experienced the onset of menses on post-op day 1 (post-SAH day 3).

Postoperatively, she had a slight left pronator drift (which resolved by post-op day 2) and was mildly confused. TCD examination at that time showed peak velocities in the 160 cm/sec range bilaterally with mean blood velocities between 102 and 119 cm/sec. By post-op day 4 (post-SAH day 6), these had risen to peak values in the range of 175-195 cm/sec with mean velocities of over 140 cm/sec. At this time, the patient's speech was clear, but not always appropriate, exhibiting excessive familiarity. Moreover, her left drift returned. She was placed on 3% saline for hypervolemic therapy early in the day. That evening, she received estradiol.

Patient 2: This 58 year-old right-handed post-menopausal woman was found on the floor, unresponsive, by her husband. Her past medical history is significant for a right ICA aneurysm clipped in 1970.

In the emergency room, she was arousable, with a severe left hemiparesis and a right gaze preference. CT scan revealed a right-sided SAH with some intraventricular blood. An angiogram showed a 2.5cm aneurysm of the right supraclinoid ICA and the site of her previous clipping. This was presumed to be the source of the hemorrhage. A 1cm basilar summit aneurysm was also found.

Both were clipped on day 1 post-SAH. Her estradiol level upon enrollment (post-SAH day 2) was 25 pg/mL. TCD exam on post-SAH day 4 (post-op day 3) showed peak blood velocities of 180-190 cm/sec and mean velocities of

125-133 cm/sec on the right with only slightly increased velocities on the left side. She received estradiol for the first time at this point.

Patient 3: This 25 year-old woman suddenly developed a severe headache, collapsed, vomited, and lost consciousness during an argument with her family. She has a history of cocaine, heroin, alcohol and benzodiazepine abuse. She had last snorted cocaine that morning.

On presentation to another hospital she was lethargic. Her neurological exam was nonfocal. Moderate nuchal rigidity was present. A lumbar puncture returned bloody CSF. A CT scan revealed SAH in the basilar cisterns and the right sylvian fissure. Cerebral angiography disclosed the presence of two aneurysms - one of the right superior hypophyseal artery and one at the bifurcation of the right internal carotid artery.

She was transferred to our institution and underwent clipping of both aneurysms on post-SAH day 2. Intraoperative angiography after clipping demonstrated good flow through the right ICA, MCA, and ACA. Her estradiol level upon enrollment (post-SAH day 4) was 18 pg/mL.

Postoperatively, she developed a severe left-sided hemiparesis, left-sided neglect and right gaze preference. CT scan showed a wedge-shaped right parietal infarct, and a large amount of right hemispheric cerebral edema resulting in right-to-left shift and effacement of the basilar cisterns. TCD exam on post-SAH day 4 showed peak velocities on the right side in excess of 250 cm/sec. Mean velocities ranged from 135-186 cm/sec. The left side could not be insonated. At this time she was given estradiol.

Chapter 6: Results of the Pilot Study

The three women who developed spasm received a total of 4 doses of estrogen early in their hospital course. Mean velocity tended to decrease an average of 23 cm/sec (range 18-27) by 120 minutes after the administration of estradiol. The plot of mean blood velocity versus time for each trial is shown in figure 3.

Using a paired t-test, the decrease in mean velocity from baseline was statistically significant beginning at 25 minutes post-administration ($p=0.039$). At each subsequent measurement point throughout the 2 hour monitoring period after estradiol administration, this difference remained statistically significant (table 1).

In 2 additional instances, women received estradiol greater than 6 days after their hemorrhage. The mean velocity in these cases was not significantly altered by estradiol.

Neither the pulsatility index (table 3) nor the peak blood flow velocity (table 2) demonstrated a significant change from baseline measurements. This was true whether the estradiol was administered early or late (>6 days post-SAH) in the course of spasm.

Estradiol levels in the 9 women enrolled did not appear to correlate with the development of vasospasm. While the women who did develop spasm exhibited low (<30 pg/mL) estrogen levels, other subjects had equivalent serum estrogen levels and remained free of spasm. Moreover, among the asymptomatic women, several experienced sharp drops in their estrogen level without developing spasm.

Figures 4 through 11 show TCD ultrasound tracings from the treated women. The baseline exams demonstrate varying patterns and degrees of vasospasm. After administration of estradiol, the mean velocities in all 3 women decrease from their baseline levels.

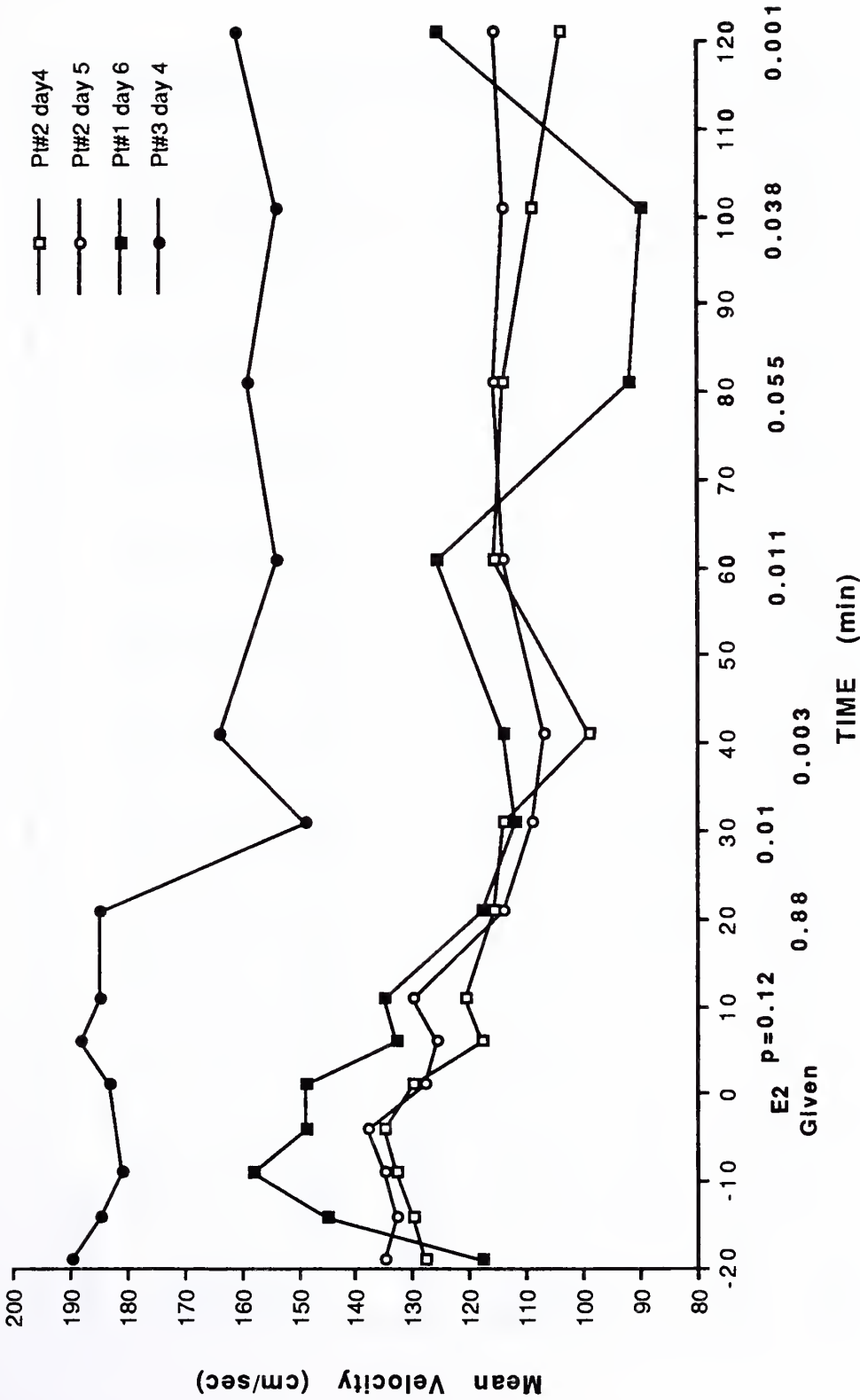


Figure 3: Mean Velocity Vs. Time <6d post-SAH

Mean velocities from 4 trials conducted in the 3 study patients who developed vasospasm are shown. The p values for the difference between baseline mean velocity and the mean velocities at each time point are also presented. The decrease in mean velocity becomes significant 30 minutes after administration (p=0.01) and remains significantly decreased compared to baseline throughout the 120 min monitoring period.

ALL TRIALS												
	TIME											
Baseline	5	10	15	20	25	30	35	40	60	80	100	120
Patient 1	148.3	133	145	116	114	110	128	112	114	90	88	124
Patient 2	129.2	116	116	114	121	112	107	97	114	112	107	102
Patient 2	131.8	128	116	112	116	107	109	105	112	114	112	114
Patient 3	204	214	207	207	212	205	200	205	210	211	205	207
Patient 1	147.4	121	128	114	155	169	157	136	135	123	123	113
Patient 3	182.75	186	183	183	164	147	145	162	152	157	152	159
p Value	0.3902	0.7232	0.0792	0.051	0.1856	0.1595	0.0617	0.014	0.03	0.046	0.024	0.011
Post SAH Day <6												
	TIME											
Baseline	5	10	15	20	25	30	35	40	60	80	100	120
Patient 1	148.3	133	145	116	114	110	128	112	114	90	88	124
Patient 2	129.2	116	116	114	121	112	107	97	114	112	107	102
Patient 2	131.8	124	128	116	116	107	109	105	112	114	112	114
Patient 3	182.75	186	183	183	164	147	145	162	152	157	152	159
p Value	0.1437	0.1249	0.1056	0.0882	0.039	0.01	0.008	0.003	0.011	0.055	0.038	0.001
Post SAH Day >6												
	TIME											
Baseline	5	10	15	20	25	30	35	40	60	80	100	120
Patient 1	204	214	207	207	212	205	200	205	210	211	205	207
Patient 3	147.4	121	157	128	114	155	169	157	135	123	123	113
p Value	0.9423	0.013	0.5977	0.557	0.016	0.4705	0.7513	0.5557	0.7869	0.6779	0.5261	0.5554

Table 1: Mean Velocity Data (cm/sec)

ALL TRIALS													
	TIME												
Baseline	5	10	15	20	25	30	35	40	60	80	100	120	
Patient 1	244	171	186	181	152	164	132	157	145	155	119	133	164
Patient 2	192	174	181	179	179	181	176	169	155	176	169	169	174
Patient 2	190.2	181	188	181	169	186	174	174	169	174	181	171	183
Patient 3	239.4	253	253	243	253	231	245	233	236	253	262	277	255
Patient 1	181.6	152	190	167	152	214	202	198	169	167	148	151	142
Patient 3	239.5	248	250	250	245	257	241	241	233	226	248	248	248
p Value 0.2206 0.5819 0.1667 0.2201 0.5047 0.4419 0.2501 0.1174 0.1934 0.1989 0.3116 0.2216													
Post SAH Day <6													
	TIME												
Baseline	5	10	15	20	25	30	35	40	60	80	100	120	
Patient 1	244	171	186	181	152	164	132	157	145	155	119	133	164
Patient 2	192	174	181	179	179	181	176	169	155	176	169	169	174
Patient 2	190.2	181	188	181	169	186	174	174	169	174	181	171	183
Patient 3	239.5	248	250	250	245	257	241	241	233	226	248	248	248
p Value 0.2832 0.3846 0.243 0.2813 0.3333 0.3391 0.2049 0.1683 0.1942 0.2197 0.257 0.3009													
Post SAH Day >6													
	TIME												
Baseline	5	10	15	20	25	30	35	40	60	80	100	120	
Patient 1	239.4	253	243	253	231	245	233	236	253	262	277	255	
Patient 3	181.6	152	190	167	152	214	202	198	167	148	151	142	
p Value 0.7742 0.1478 0.6539 0.7742 0.6615 0.3294 0.7369 0.3322 0.9774 0.877 0.9349 0.7389													

Table 2: Peak Velocity Data (cm/sec)

<u>ALL TRIALS</u>													
	TIME												
Baseline	5	10	15	20	25	30	35	40	60	80	100	120	
Patient 1	1.04	0.52	0.85	0.45	0.5	1.05	0.33	0.43	0.49	0.97	0.67	0.74	0.58
Patient 2	0.82	0.82	0.86	0.89	0.91	0.87	1.07	0.97	0.86	0.86	0.97	0.96	1.03
Patient 2	0.77	0.78	0.97	0.85	0.83	1.38	0.95	1.34	0.88	0.89	0.88	0.91	0.97
Patient 3	0.27	0.21	0.49	0.35	0.55	0.72	0.3	0.84	0.29	1.16	0.38	0.85	1.02
Patient 1	0.4	0.41	0.41	0.8	0.91	0.86	0.33	0.93	0.45	0.65	0.34	0.42	0.43
Patient 3	0.51	0.59	0.54	0.58	0.78	1.04	0.82	1.08	0.76	0.97	1.14	0.78	
p Value	0.4141	0.4346	0.963	0.6064	0.026	0.846	0.231	0.7943	0.1343	0.5755	0.2193	0.3445	
<u>Post SAH Day <6</u>													
	TIME												
Baseline	5	10	15	20	25	30	35	40	60	80	100	120	
Patient 1	1.04	0.52	0.85	0.45	0.5	1.05	0.33	0.43	0.49	0.97	0.67	0.74	0.58
Patient 2	0.82	0.82	0.86	0.89	0.91	0.87	1.07	0.97	0.86	0.86	0.97	0.96	1.03
Patient 2	0.77	0.78	0.97	0.85	0.83	1.38	0.95	1.34	0.88	0.89	0.88	0.91	0.97
Patient 3	0.51	0.59	0.54	0.58	0.78	1.04	0.82	1.08	0.76	0.97	1.14	0.78	
p Value	0.4946	0.819	0.5763	0.6382	0.1858	0.8308	0.7066	0.8651	0.2964	0.6449	0.4808	0.7706	
<u>Post SAH Day >6</u>													
	TIME												
Baseline	5	10	15	20	25	30	35	40	60	80	100	120	
Patient 1	0.27	0.21	0.49	0.35	0.55	0.72	0.3	0.84	0.29	1.16	0.38	0.85	1.02
Patient 3	0.4	0.41	0.41	0.8	0.91	0.86	0.33	0.93	0.45	0.65	0.34	0.42	0.43
p Value	0.6051	0.4711	0.3743	0.1804	0.007	0.7578	0.023	0.2578	0.3257	0.8179	0.4781	0.4745	

Table 3: Pulsatility Index Data

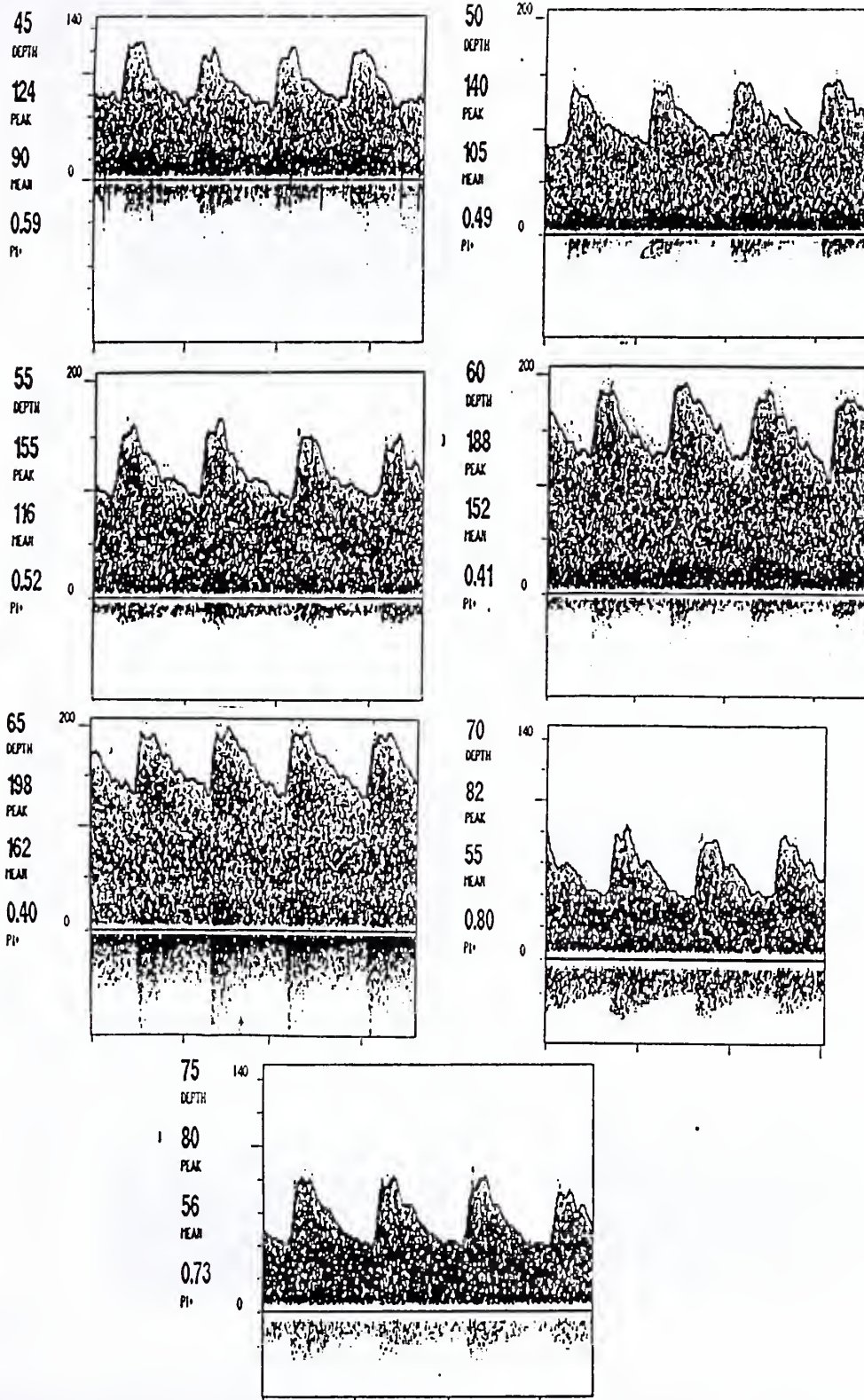


Figure 4: TCD Ultrasound of patient 1 on post-SAH day #6

The figure shows TCD tracings at depths ranging from 45mm to 75mm. Flow velocities indicative of vasospasm are observed at 60mm depth and 65mm. This corresponds to the MCA M₁ segment or the distal ICA.

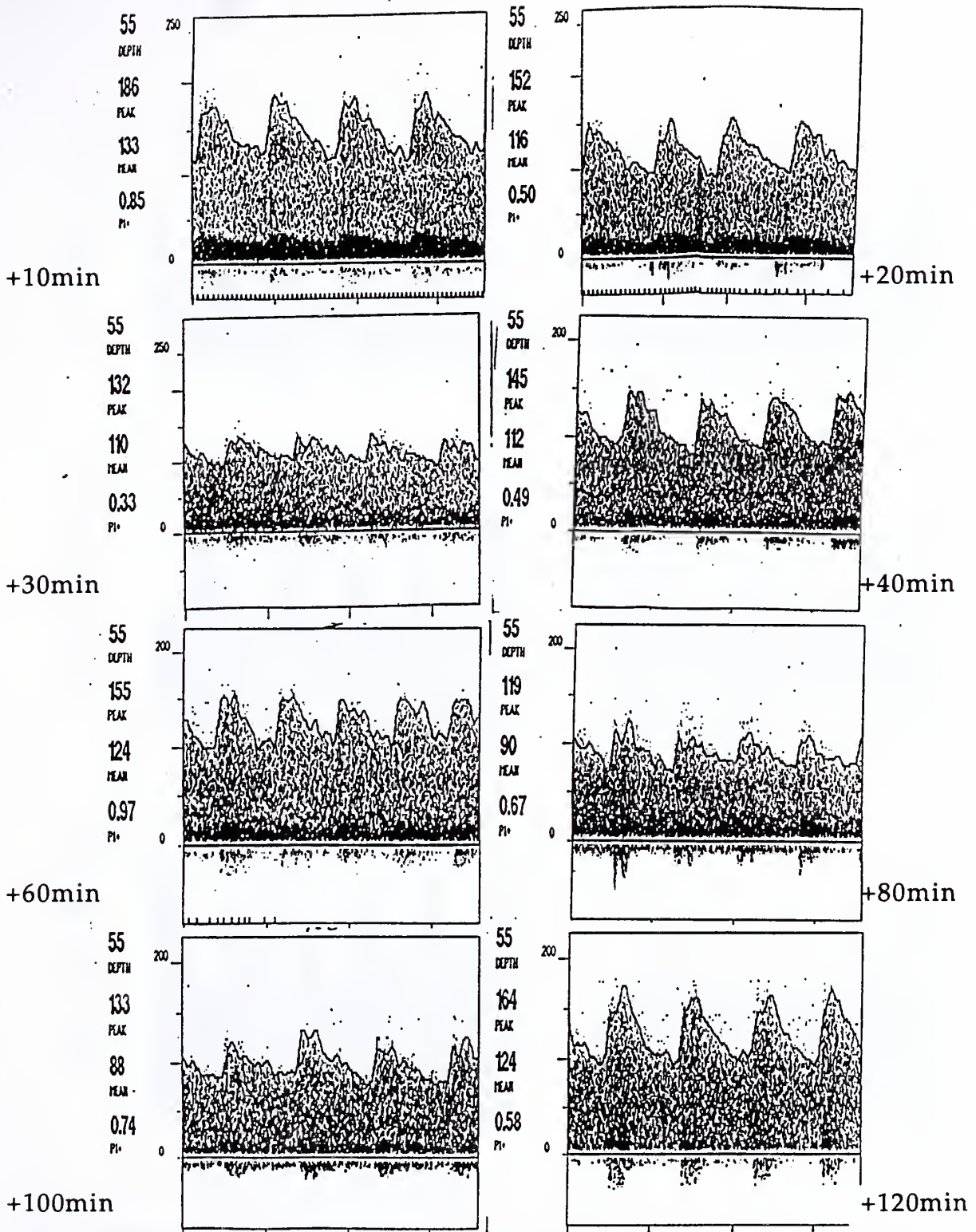


Figure 5: TCD Ultrasound of Patient 1 after Estradiol Administration on post-SAH day #6

The figure presents sequential TCD tracings at 55mm depth after estradiol administration. Mean flow velocities decrease and reach a nadir of 90 cm/sec before rising again 120 min after the estradiol was given. Baseline was 148 cm/sec.

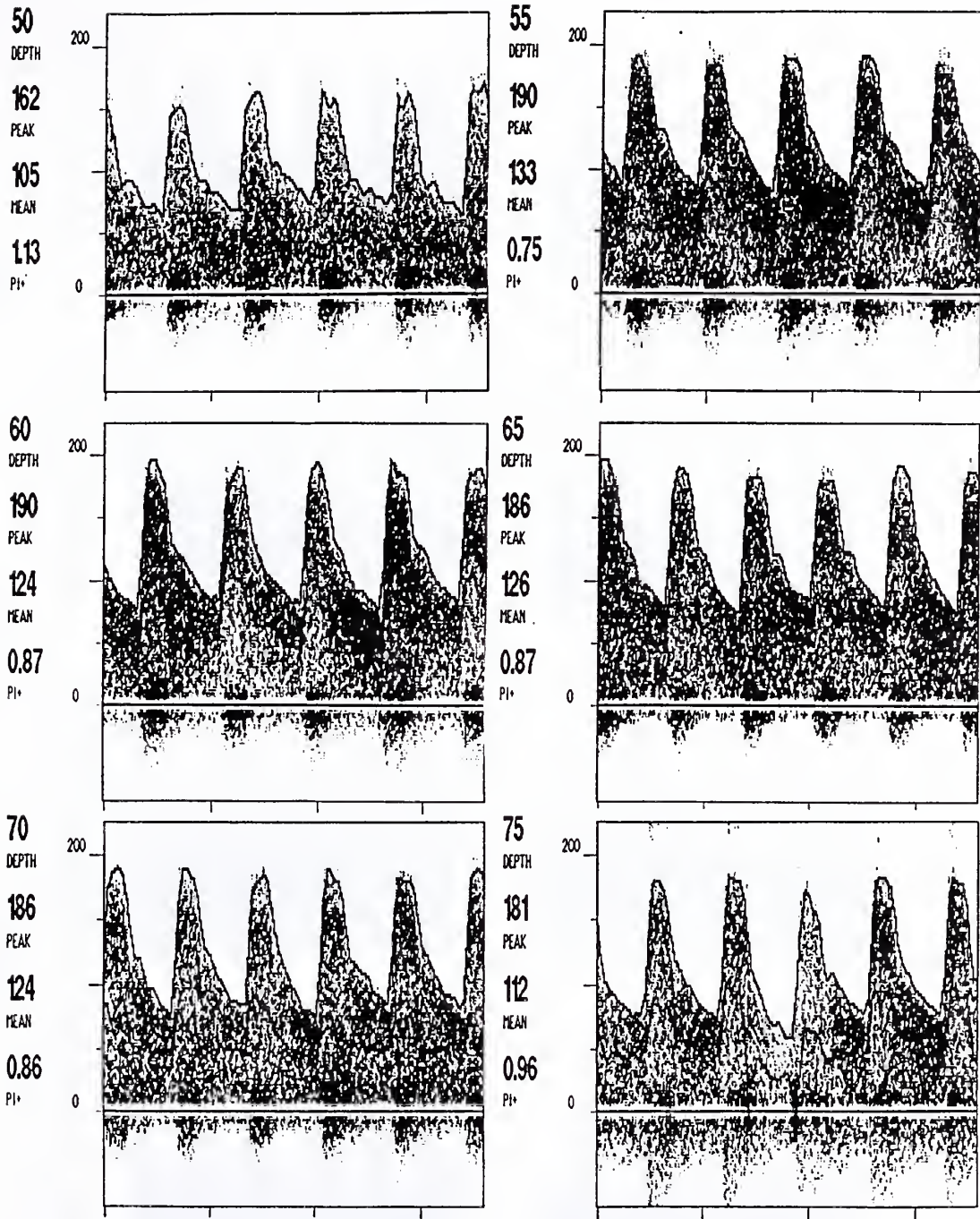


Figure 6: TCD Ultrasound of patient 2 on post-SAH day #4

The figure shows TCD tracings at depths ranging from 50mm to 75mm. Flow velocities indicative of vasospasm are observed from 55mm through 70mm depth. This corresponds to the MCA, ICA and possibly the AComm also.

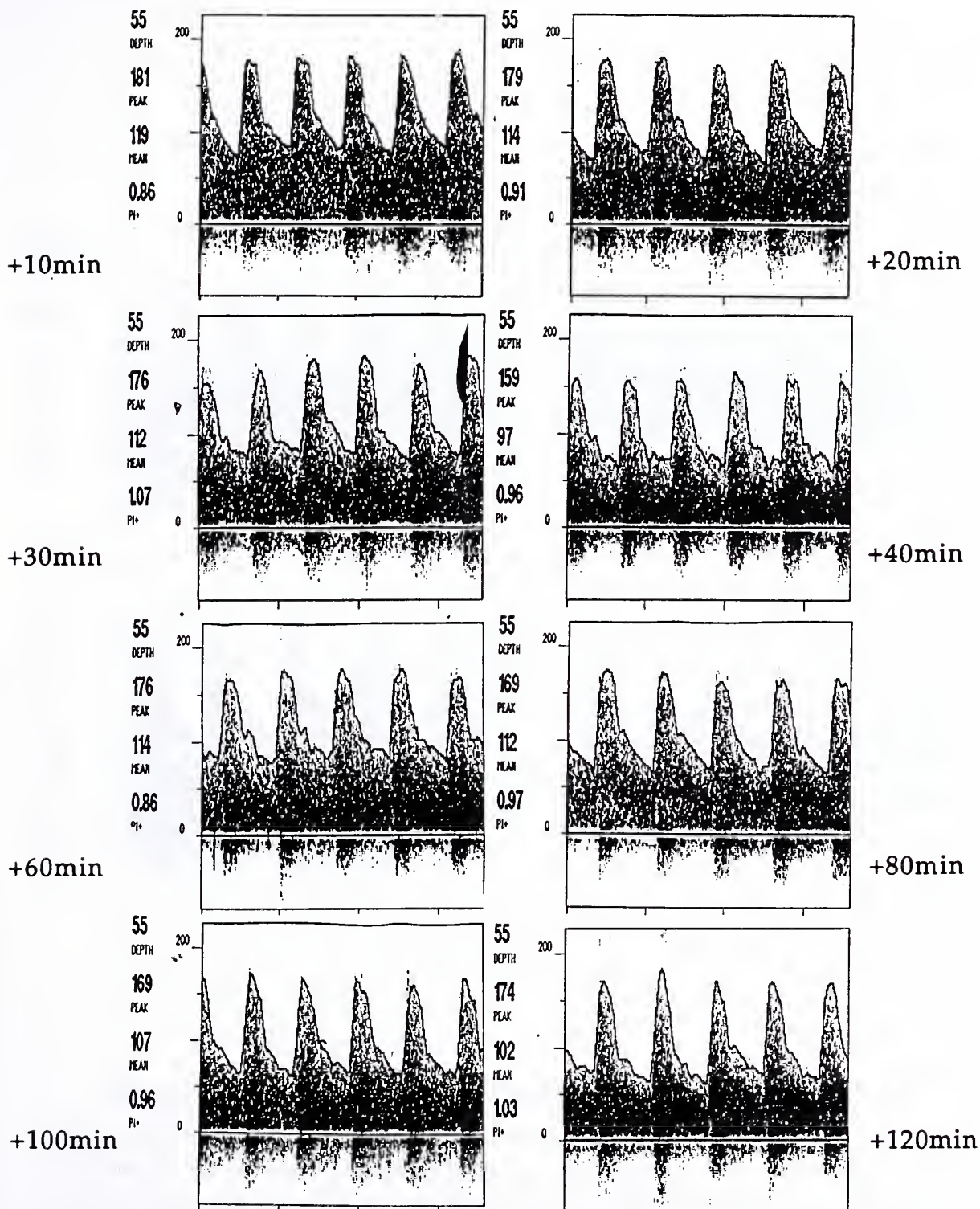


Figure 7: TCD Ultrasound of Patient 2 after Estradiol Administration on post-SAH day #4

The figure presents sequential TCD tracings at 55mm depth after estradiol administration. Mean flow velocities decrease and reach a nadir of 97 cm/sec and remain below baseline 120 min after the estradiol was given. Baseline was 129cm/sec.

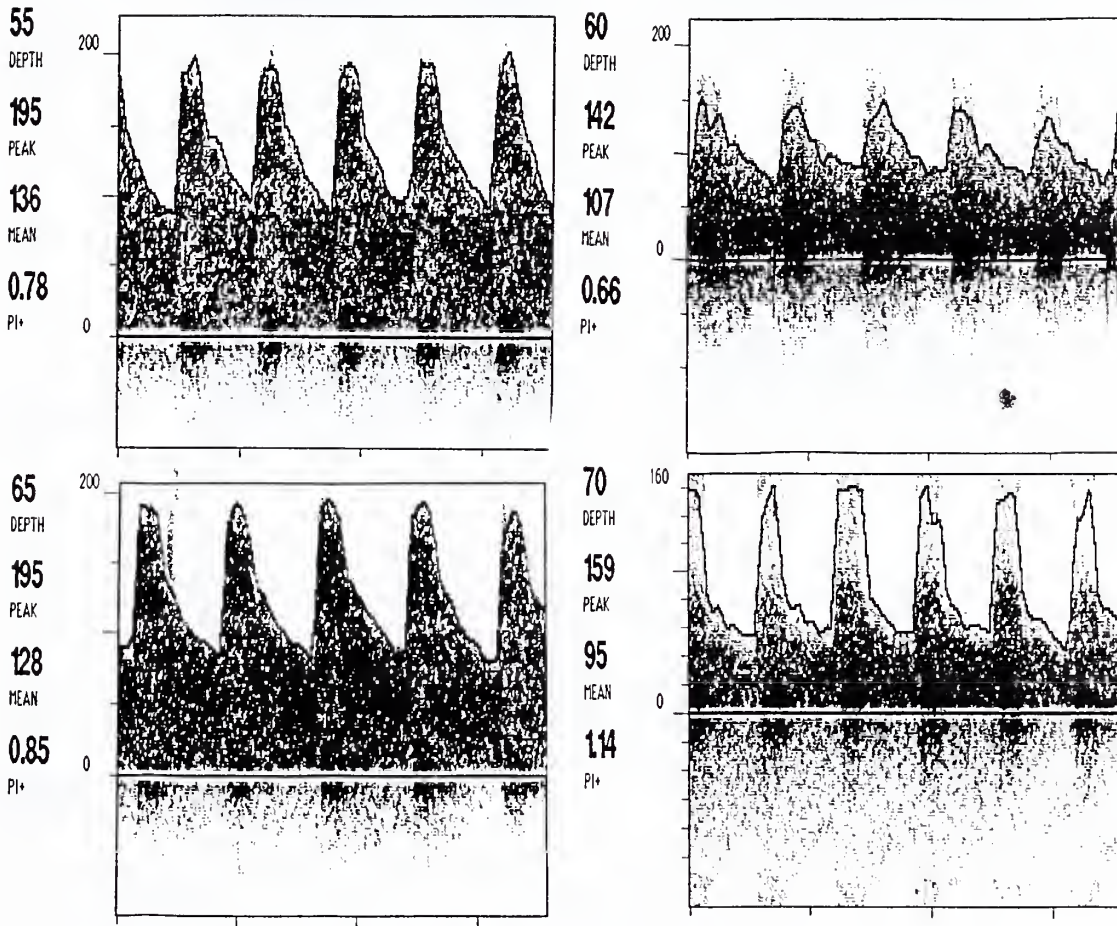


Figure 8: TCD Ultrasound of patient 2 on post-SAH day #5

The figure shows TCD tracings at depths ranging from 55mm to 70mm. Flow velocities indicative of vasospasm are observed at 55mm and 65mm depth. This represents segmental spasm in the MCA.

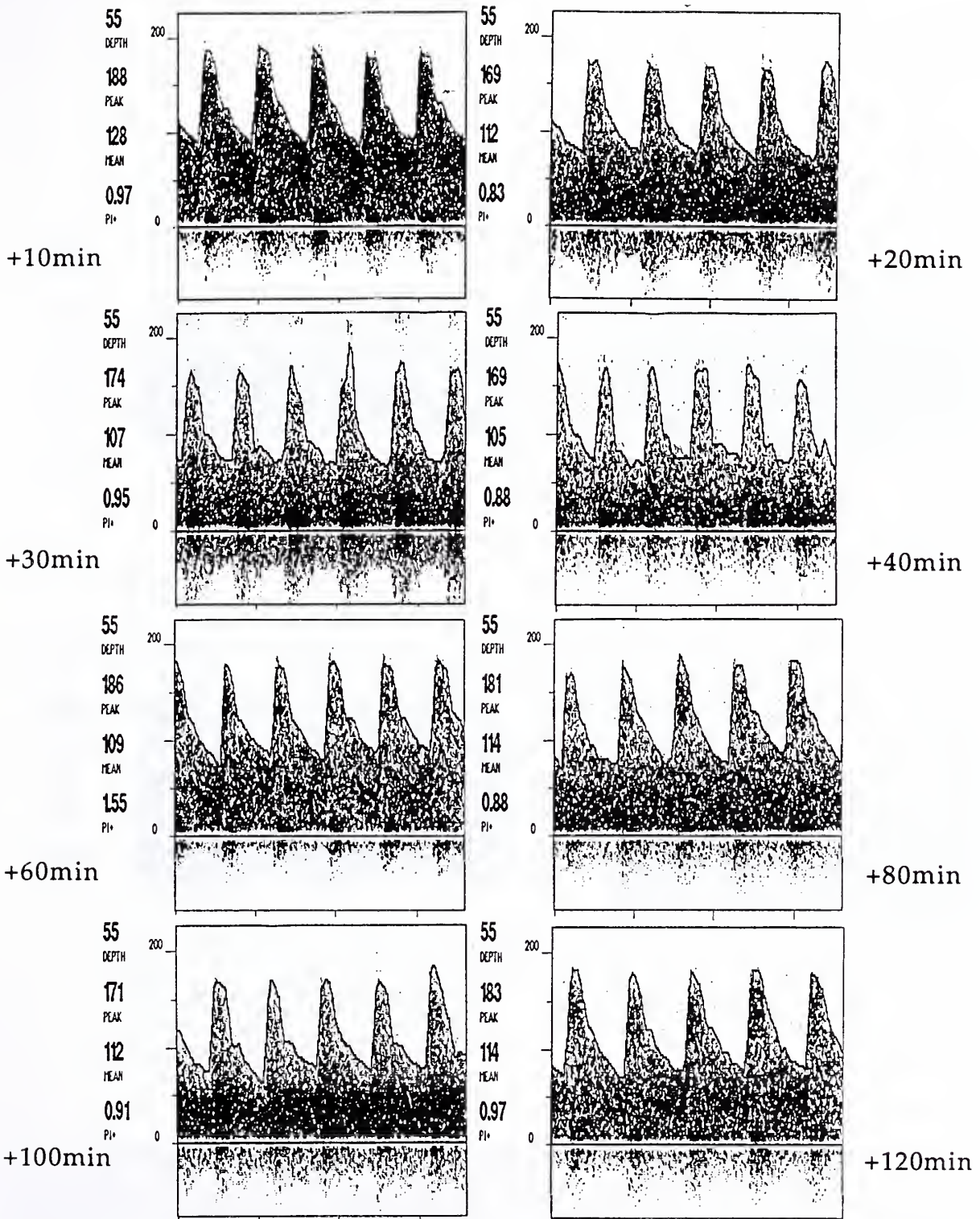


Figure 9: TCD Ultrasound of Patient 2 after Estradiol Administration on post SAH day #5

The figure presents sequential TCD tracings at 55mm depth after estradiol administration. Mean flow velocities decrease to a nadir of 97 cm/sec and remain below baseline 120 min after the estradiol was given. Baseline was 132 cm/sec.

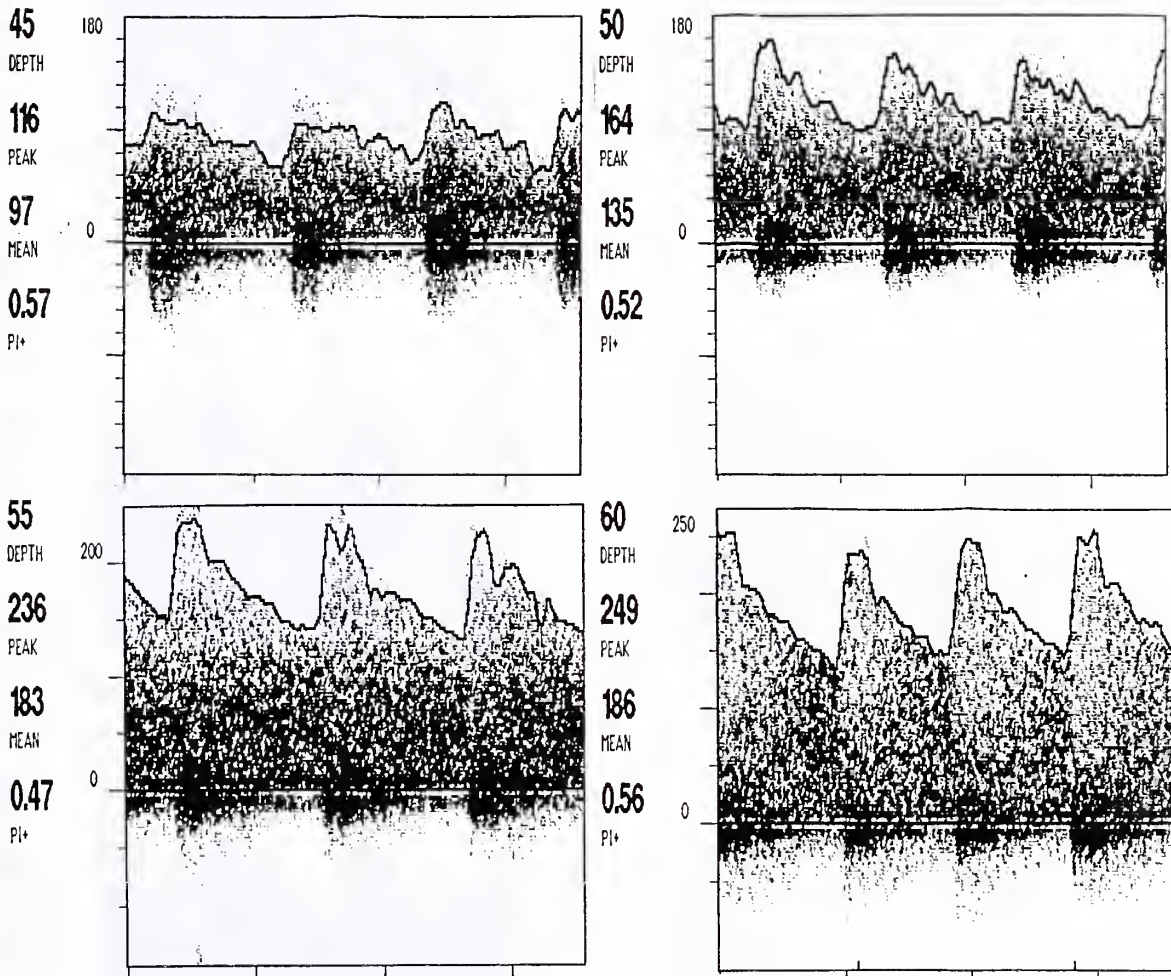


Figure 10: TCD Ultrasound of patient 3 on post-SAH day #4

The figure shows TCD tracings at depths ranging from 45mm to 60mm. Flow velocities indicative of severe vasospasm are observed at 55mm and 60mm depth. The patient's anatomy limited this exam.

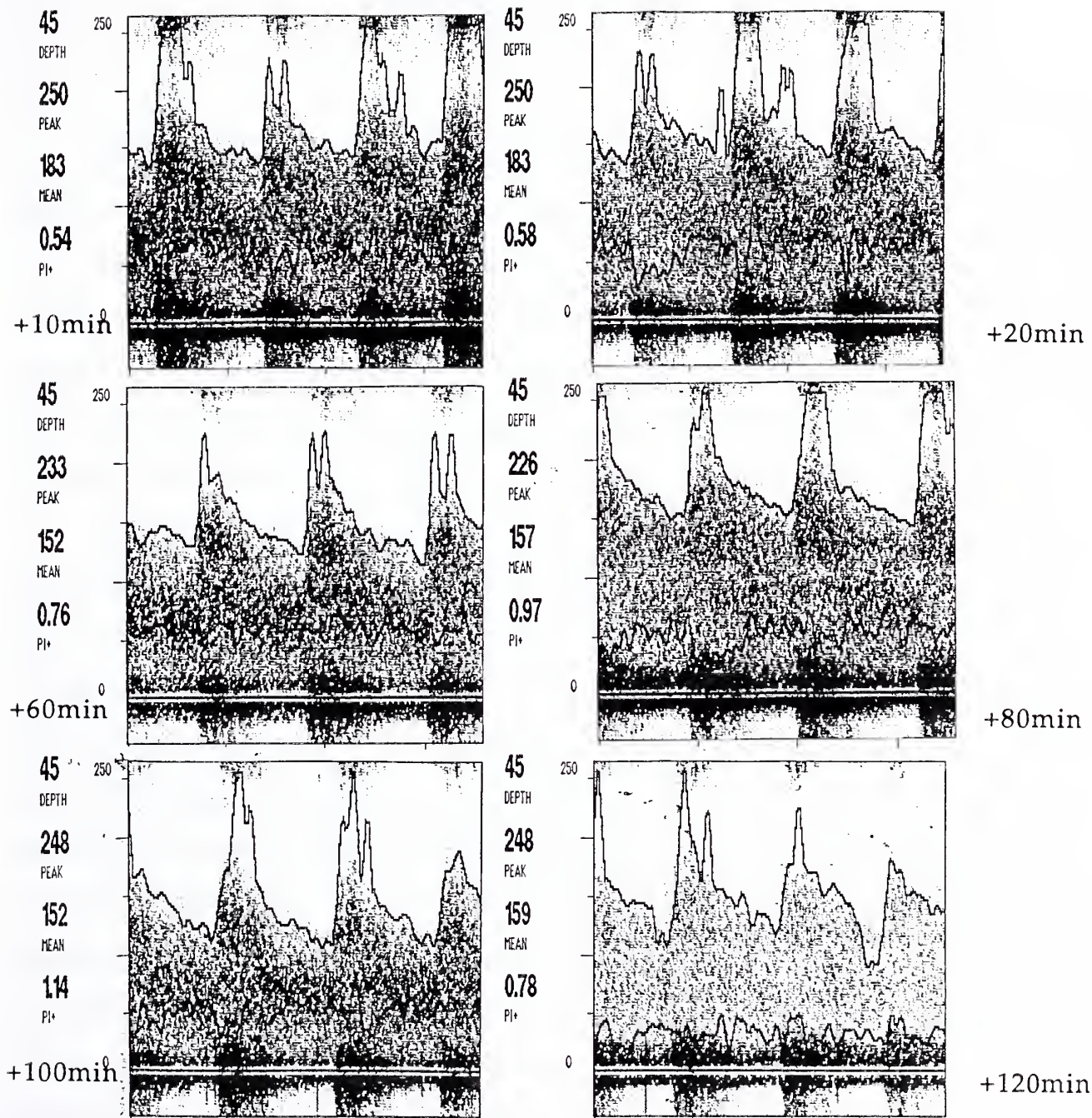


Figure 11: TCD Ultrasound of Patient 3 after Estradiol Administration on post SAH day #4

The figure presents sequential TCD tracings at 45mm depth after estradiol administration. Mean flow velocities decrease to a nadir of 152 cm/sec and remain below baseline 120 min after the estradiol was given. Baseline was 183 cm/sec.

Chapter 7: Discussion

This pilot study indicates that estradiol may have the capacity to aid in alleviating cerebral vasospasm after subarachnoid hemorrhage. The 3 women we treated all demonstrated a decrease in the mean flow velocity in response to estradiol administration. This response had its onset approximately 25 to 30 minutes after administration and lasted through the 2 hour monitoring period. This is the first study to investigate and report an effect of estradiol on vasospasm after aneurysmal rupture.

As presented earlier, SAH leads to impairment of endothelium-dependent vasodilation. Estradiol appears to cause the release of increased amounts of nitric oxide. The administration of inhibitors of nitric oxide synthesis can interfere with estradiol-induced vasodilatation. By facilitating the release of nitric oxide, estradiol would tend to cause vascular smooth muscle relaxation and relief of spasm. The lag time to onset that we experienced agrees with the literature discussed in previous chapters. The 30-minute time period needed for estradiol to affect the NO system is well established in *in vitro*, as well as clinical, studies. These results indicate that we may be observing endothelium-dependent relaxation. Since estradiol's effect as a calcium channel antagonist has its onset approximately 10 to 15 minutes after administration, we cannot definitely state that the effect we observed is due to just one or a combination of these mechanisms.

We have also had a limited experience administering estradiol to women who are further along in the course of vasospasm (after post-SAH day 6). In the few trials run under these conditions, no significant change in mean blood

velocity was observed. It is known that by day 7 after aneurysmal rupture chronic inflammatory changes and medial smooth muscle hypertrophy have begun to occur in the spastic artery. Cerebral autoregulation has been shown to be defective at this point in the course of spasm. In addition, vasodilatory capacity as measured by acetazolamide challenge is also reduced one week after SAH. These changes may nullify estrogen's effect on the vessels. Further trials are required to properly characterize this finding.

Some conditions that involve vasomotor instability, such as "Syndrome X" (microvascular angina), menopause and possibly Reynaud's phenomenon and catamenial migraine, have been associated with a deficiency of endogenous estrogens. One patient experienced menses just prior to developing vasospasm and all 3 women had low estrogen levels (<50pg/mL). The possibility that decreased estrogen levels may aid in the development of or exacerbate vasospasm deserves investigation.

We will investigate the relationship between estradiol levels and the development and the severity of vasospasm. Longstreth examined the menopausal status of women with subarachnoid hemorrhage(164). He found that premenopausal women were at a substantially reduced risk for hemorrhage (odds ratio 0.24). Moreover, hormone replacement therapy led to a risk reduction (odds ratio 0.47) in postmenopausal women. Interestingly, 74% of the premenopausal women were within one week of menstruation, the time of lowest estradiol levels. As our study population grows, we will not only be able to confirm this finding in our own cohort, but also to determine if acute drops in the estradiol level tend to precipitate vasospasm.

However, among our current patient population, the serum estradiol level and the change in this level following subarachnoid hemorrhage does not

seem to be predictive of the development of spasm. A larger sample size will enable us to provide a definite answer to these questions.

We are still enrolling patients in the hopes of further solidifying our data as well as elucidating more information about the effect we have observed. We have already observed a decrease in velocities that lasts throughout our monitoring period. In future studies, women will be monitored with TCD every 20 minutes until estradiol's effect subsides and velocities rise to their pretreatment levels. This will help us to further characterize the duration of estradiol's action in cerebral vasospasm.

In addition, once the velocities return to their baseline level, subjects will be immediately rechallenged with another 1mg of sublingual estradiol so that we may demonstrate a reproducible effect, as well as any enhancement of inhibition of the effect with rechallenge.

A double-blinded placebo-controlled trial of estradiol supplementation is needed to fully determine the therapeutic efficacy of estradiol. For this purpose, women would receive either 1mg sublingual estradiol every 12 hours or a placebo. Clinical parameters (neurological exam), as well as TCD flow velocities will be monitored in both groups.

The finding presented here is encouraging for the possible use of estradiol replacement to ameliorate the development of early vasospasm after SAH. Estradiol is already in wide use for the prophylactic prevention of catamenial migraine, vasomotor instability associated with the menopause, and for Syndrome X. Eventually, it may be possible to administer estrogen prophylactically to women diagnosed with subarachnoid hemorrhage in an effort to reduce the morbidity and mortality of this condition.

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