Evolution of the treatment of cerebral vasospasm

SCOTT Y. RAHIMI, M.D., JOHN H. BROWN, B.S., SAMUEL D. MACOMSON, M.D., MICHAEL A. JENSEN, M.S., AND CARGILL H. ALLEYNE JR., M.D.

Department of Neurosurgery, Medical College of Georgia, Augusta, Georgia

✓Cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH) is a disease process for which the lack of effective treatments has plagued neurosurgeons for decades. Historically, successful treatment after SAH in the acute setting was often followed by a rapid, uncontrollable deterioration in the subacute interval. Little was known regarding the nature and progression of this condition until the mid-1800s, when the disease was first described by Gull. Insight into the origin and natural history of cerebral vasospasm came slowly over the next 100 years, until the 1950s. Over the past five decades our understanding of cerebral vasospasm has expanded exponentially. This newly discovered information has been used by neurosurgeons worldwide for successful treatment of complications associated with vasospasm. Nevertheless, although great strides have been made toward elucidating the causes of cerebral vasospasm, a lasting cure continues to elude experts and the disease continues to wreak havoc on patients after aneurysmal SAH.

KEY WORDS • cerebral vasospasm • cerebrovascular disease • history of neurosurgery

SUBARACHNOID hemorrhage after CVAs such as aneurysm rupture is a disease that has been well known to physicians for decades. A common complication following aneurysmal SAH is cerebral vasospasm, which can take place in up to half of patients after bleeding occurs (Video 1). Neurological deficit or death can occur in up to 20% of patients if their cerebral vasospasm is left untreated. In fact, the most common cause of death and disability in patients with SAH in a subacute setting is delayed cerebral ischemia caused by arterial spasm. Due to the devastating nature of vasospasm, researchers and clinicians have spent years and countless resources attempting fully to understand the pathophysiological origins of this process in the hope of finding a cure. Vasospasm is a relatively newly recognized disease process that has only been scrutinized over the past 50 years. However, the roots of our awareness can be traced back to a century and a half ago, when an English physician first described symptoms of cerebral vasospasm in a patient who had suffered from a ruptured aneurysm.

Video 1. Movie showing vasospasm of a cerebral vessel after SAH. Click here to view with Windows Media Player and a broadband connection and here to view with RealPlayer.

Historical Perspective on Vasospasm

Awareness of cerebral vasospasm began nearly 150 years ago when an English physician by the name of Gull described this fatal illness. His patient was a young woman who suffered a stroke, with acute deterioration in her neurological status. Over the next several days the patient remained ill and was in a comatose state. On the 4th day after the onset of her illness, she was more alert and was able to utter words and recognize family. On the 5th day, however, her condition deteriorated rapidly, her pupils became fixed and dilated, and she died. At the time of autopsy a ruptured middle cerebral artery aneurysm was identified, which was surrounded by a large clot in the sylvian fissure with associated softening of that hemisphere. Gull’s findings are consistent with a CVA from a ruptured aneurysm followed by infarction due to cerebral vasospasm. The significance of this description and its role in the recognition of vasospasm was not fully appreciated until the 1920s.

The next important observation that helped lay the foundation for our understanding of cerebral vasospasm occurred in 1925, as reported by the physiologist Florey. He observed that feline cerebral arteries subjected to mechanical and electrical stimulation underwent local spasm. In 1944, Zucker described substances in blood serum that stimulated smooth-muscle contraction and concluded that lysed red blood cells have vasoconstrictive properties.

Another great contribution that would later assist in solving the mystery of vasospasm came with the discovery of cerebral angiography in 1927. Egaz Moniz was the first person to perform a cerebral angiogram successfully in a living person. He was in fact the first individual to publish a case involving an aneurysm that could be visualized using angiography. It is noteworthy that it was not until 1937 that Dandy described the first direct clip occlusion of an intracranial aneurysm.

Abbreviations used in this paper: CT = computerized tomography; CVA = cerebrovascular accident; SAH = subarachnoid hemorrhage.
Further insight into the pathogenesis of cerebral vasospasm was gained by two other investigators in the 1940s. In 1949, Jackson\(^1\) injected a variety of blood products into the cisterna magna of dogs. He noted that the red blood cell was the substance that elicited the greatest meningeal response. In the same year, Robertson\(^2\) reviewed a large series of ruptured aneurysm cases. He found evidence of cerebral infarction in the presence of patent cerebral vessels that were surrounded by blood clot. He hypothesized that the ischemia was due to temporary spasm of the supply vessels rather than compression by the aneurysm.

Progress in Understanding Vasospasm

Initial Progress

The 1950s marked a pivotal time in our understanding of cerebral vasospasm. Up to then, there had been no hard evidence demonstrating this entity. In 1951, however, a paper by Ecker and Riemenschneider\(^3\) provided evidence of vasospasm. These authors described angiographically confirmed spasm of cerebral arteries and its relationship to cerebral aneurysms. Vasospasm was defined as a change in caliber of arterial vessels based on two consecutive cerebral angiograms performed under identical conditions at different time intervals.\(^4\) Ecker and Riemenschneider presented six cases of vasospasm, all in patients after SAH. Vasospasm was greatest near the site of the ruptured aneurysm correlating to the area with the largest amount of blood products. These authors also noted that vasospasm was a self-limited process, because it was not seen in any angiograms performed 26 days after SAH. The modern era of recognition and treatment of vasospasm started with their description, “It is probable that arterial spasm plays an important role following spontaneous rupture of saccular aneurysms of or near the circle of Willis.”

As knowledge of vasospasm and evidence suggesting its role in neurological disease were becoming more widespread, efforts to treat this disease process became a priority. Neurologist Denny-Brown\(^5\) observed that hypotension could be disastrous for patients following CVA and recommended raising the systolic blood pressure to avoid neurological deficits. He reported cases in which neurological deterioration occurred due to hypotension superimposed on narrowing of major blood vessels. Although Denny-Brown did not directly correlate clinical deterioration from cerebral hypotension with vasospasm, he did provide evidence linking changes in systolic blood pressure with neurological symptoms in patients with CVAs.

Consequences of Vasospasm

By the 1960s the consensus was that vasospasm was a cause of high rates of morbidity and mortality in patients after CVAs. In 1964, Stornelli and French\(^6\) reported on their experience in treating 28 patients after SAH from a ruptured aneurysm. The appearance of vasospasm on angiographic studies was much more common in patients who died after surgery than in those who recovered postoperatively. These authors concluded that intracranial vasospasm was a key factor in the determination of outcome after aneurysmal SAH.

In 1965, Alcock and Drake\(^7\) also presented a series of patients with SAH in whom postoperative angiograms were obtained. Vasospasm was seen in 51% of patients who underwent surgery within 3 days of hemorrhage, in 61% who received surgical treatment 6 to 10 days after SAH, and in 9% of patients who underwent surgery 10 days post-SAHA. The interval between SAH and angiography was 3.7 days in patients with and 6.9 days in those without vasospasm. The idea that vasospasm was associated with high morbidity and/or mortality rates and the misconception that it occurred at a time closer to the occurrence of SAH led to the theory advocating delayed surgical intervention for ruptured aneurysms. Further recommendations regarding surgical intervention for the treatment of aneurysms came in 1967. This research was completed by Kennedy,\(^8\) who concluded that significant amounts of blood could be removed from the subarachnoid space by irrigation, which in turn could decrease the risk of vasospasm.

Controlling Vasospasm

The 1970s were marked by a large influx of literature providing insight into vasospasm. Suzuki and associates\(^9\) reported only a slight difference in outcome among surgically treated patients with and without vasospasm in a series of 44 cases. This led to their faulty recommendation that surgical intervention could be performed at any time after SAH, regardless of the presence or absence of vasospasm. In 1975 a multiple regression analysis was conducted to predict mortality rates post-SAH by using data obtained in 135 patients with this disorder who were treated during a 5-year period at the University of Alberta.\(^10\) Important factors predicting 2-month mortality rates included results of initial neurological examination, neurological status at surgery, shortened time interval to surgery, advanced age, and hypertension.

Different treatment modalities to combat vasospasm were described during this period. In 1972, Wise and colleagues\(^11\) showed that neurological deficits could be reversed with the use of vasopressors. Improvement in neurological status was noted when systolic blood pressure was raised to a range of 150 to 170 mm Hg and diastolic pressure was raised to 85 to 100 mm Hg. Several years later, other authors, including Kosnik and Hunt\(^12\) and Giannotta, et al.,\(^13\) were also able to reverse neurological deficits after ischemia due to vasospasm by elevating central venous pressure with whole blood, plasma, or albumin. This era marked the beginning of triple-H therapy (also called hypertension, hypervolemia, and hemodilution therapy) as it is known today. As detailed by Weir\(^14\) in his history of cerebral vasospasm, further efforts to combat this disorder came in 1979, when Allen showed that acute and chronic vasospasm in dogs could be reversed by the calcium antagonist nifedipine. Based on this observation, a human trial of another calcium antagonist, nimodipine, was initiated. Allen, et al.,\(^15\) found that a neurological deficit due to vasospasm occurred in eight of 60 patients receiving placebo compared with one of 56 receiving nimodipine.

To this point, no consensus had been reached regarding the timing of aneurysm surgery for avoidance of vasospasm. In 1976, Suzuki and Yoshimoto\(^16\) analyzed more than 400 aneurysm cases treated during the 1970s. They found excellent outcomes when surgery was performed during the first few days after SAH. They hypothesized that early surgery decreased the likelihood of vasospasm by re-
moving blood products surrounding cerebral arteries. Further evidence confirming the timing of vasospasm was provided by Weir and colleagues\(^{19}\) in 1978. Based on the vessel diameter demonstrated on angiographic studies obtained at different time periods, these authors showed that vasospasm began on approximately the 3rd day after SAH and was gone by Day 12. Patients who had a greater degree of vasospasm also did worse clinically and had a higher mortality rate.

**Vasospasm and Imaging**

With technological advances, tools like CT and positron emission tomography studies began to be used more often in neurosurgical settings. Katada, et al.\(^{16}\) were the first to describe the relationship between the size of the blood clot in the basilar cisterns on CT scans and subsequent demonstration of vasospasm on angiographic studies. Takemae, et al.\(^{31}\) confirmed these findings with their study in 1978. Vasospasm was seen on cerebral angiograms in 83% of patients in whom hyperdensity was demonstrated in the basilar cisterns on CT scans, whereas no vasospasm was seen in patients without SAH on CT scans. During the same period, positron emission tomography studies obtained by Grubb, et al.\(^{12}\) revealed a fall in cerebral blood flow and cerebral metabolic rate along with an increase in cerebral blood volume in the arteries affected by vasospasm. The conclusive relationship between findings on CT scans and angiographically confirmed vasospasm was established by the publication of a study by Fisher, et al.\(^{9}\) in 1980. In this report, vasospasm was seen on angiographic studies in 5% of patients without SAH on CT scans, compared with 96% of patients in whom SAH was demonstrated. The volume of SAH was the only factor determining vasospasm.

**Molecular Basis of Vasospasm**

The role of blood products in the development of vasospasm was thoroughly scrutinized in the 1970s. Miyaoka and associates\(^{22}\) found that mixtures of blood and cerebrospinal fluid had increasing vasoactivity on canine basilar arteries after incubation for 7 days. Analysis of the solution revealed that oxyhemoglobin may have been the compound with the vasoactive properties. In 1977, a paper by Osaka\(^{24}\) further explored the relationship between vasospasm and blood breakdown products. Erythrocytes caused vasoconstriction only when they had lysed following incubation for several days. In 1984, Espinosa, et al.\(^{4}\) revealed that microsurgical application of autologous blood around the basilar arteries produced vasospasm in a primate model. Neurological deficits associated with the vasospasm developed in 5% of these animals 4 to 5 days after exposure to the implanted blood. Over the years, many other spasmogens have been implicated in the development of vasospasm. Some of these substances include histamine, eicosanoids, endothelin, and nitrous oxide.\(^{23}\) Most recently, 2-hydroxy-3-methylglutaryl-coenzyme A reductase (statins) and estrogen have been used to treat vasospasm.\(^{19,20}\) Studies have shown that the use of these compounds could lead to prevention of cerebral vasospasm.

**Modern Treatment of Vasospasm**

Today, with improved techniques for coil embolization and clip occlusion of aneurysms, a great majority of patients are successfully treated through the acute phase after SAH. External ventricular drainage initially advocated by Takahashi, et al.,\(^{30}\) and/or aggressive irrigation of the basal cisterns at surgery is generally performed. Nimodipine is routinely used as prophylaxis against delayed ischemic neurological deficits associated with vasospasm. Patients with SAH are monitored closely for signs of deterioration and possible development of vasospasm. Transcranial Doppler ultrasonography, which was first introduced by Aaslid, et al.\(^{1}\) in 1982, is often used as a noninvasive tool to assess intracranial blood flow velocities for evaluation of vasospasm. In the setting of cerebral vasospasm, in addition to triple-H therapy, angioplasty may be performed to reverse or limit ischemia caused by this disorder. This technique, first introduced in 1984 by the Russian physician Zubkov and colleagues,\(^{36}\) can be used acutely to increase the caliber of the arteries affected by spasm. Endovascular infusion of vasodilatory substances such as papaverine, or of calcium channel blockers such as verapamil, is also used in the treatment of vasospasm. Papaverine was initially used as an oral agent in 1948 to prevent cerebral ischemia.\(^{26}\) Kaku, et al.,\(^{15}\) used papaverine for intraarterial infusion in 10 patients with vasospasm in 1992. These authors observed that eight of their 10 patients showed improvement in neurological function after the procedure. In addition, based on encouraging results in recent studies, the use of statins may soon become widespread.

**Conclusions**

Advances made in the field of cerebral vasospasm during the past 50 years have significantly improved the quality of care for patients with ruptured cerebral aneurysms. In the first half of the twentieth century a slight increase in the awareness of this condition occurred, but few means of prevention were then offered. New methods of detection and treatment of vasospasm have helped reduce the incidence of delayed neurological deficits. Although a complete understanding of this disease process has not yet been gained, the use of modern tools and techniques has allowed neurosurgeons to provide a much more effective approach to managing the disorder. Research into the efficacy of proposed treatments as well as the development of new types of therapy has been ongoing in the field of neurological surgery, and the positive results that are being reported are promising for the patients of today and tomorrow. We hope that the current progress will lead to a future in which cerebral vasospasm will be a concern of the past.

**References**


