11 Delayed Cerebral Vasospasm: Current Hypotheses and Future Treatments

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11.1 INTRODUCTION

Delayed cerebral vasospasm (DCV) is the leading cause of morbidity and mortality in patients who have ruptured intracranial aneurysms and are admitted to tertiary care centers.\textsuperscript{1,2} Thick focal collections of blood visualized on a CT scan are highly predictive of the risk of DCV.\textsuperscript{3,4} The time course of the event is well established,\textsuperscript{5} although the pathophysiology has remained a puzzle for many years. Recent advances in cellular and molecular biology techniques have led to the development of new hypotheses regarding this very important clinical problem.

In some ways vasospasm is a misnomer because it implies a reactive vascular tone increase with secondary vessel narrowing. However, a critical difference between an ordinary vasospasm and the vasospasm of DCV is that vessels lose their
sensitivity to most agents acting directly on vessel walls in DCV. For example, nitric oxide and nitroprusside, among other equivalent agents, normally act directly to significantly dilate smooth muscles in vessel walls, but have little effect in DCV.\(^6,7\) An active tone increase implies a significant decrease in elasticity due to the contraction; whereas the vessel can be easily dilated with angiographic balloons (balloon angioplasty; see Chapter 12 for details).

This contrary phenomenon occurs because the tension in the vessel wall is proportional to the luminal radius; therefore, as the radius of the spastic vessel decreases, the tension in the wall also decreases. Thus, human DCV occurs in a delayed fashion, shows severe luminal narrowing which is not a vasospasm in the usual sense of active muscle contraction, and cannot be relaxed except with mechanical dilatation via angioplasty from the luminal side.

While the time course of DCV is well known, the reason the onset occurs several days (typically 5 to 7) after the initial subarachnoid hemorrhage has not been explained adequately. We will construct a presumed chain of events leading to the peculiar time course, together with a brief review of pertinent hypotheses and possible new treatment mechanisms.

### 11.2 TIME COURSE, DIAGNOSIS, AND MANAGEMENT OF DCV

DCV occurs only after a precipitating event. The most common event is a subarachnoid hemorrhage (SAH) occurring in the basal cisterns secondary to rupture of a berry aneurysm. The volume of the SAH as determined by computerized tomography (CT) scan (Fisher grade) clearly relates to the probability of DCV.\(^3\) Other causes of SAH, for example, head injury, may also precipitate DCV if the SAH is sufficiently dense.\(^8,9\)

It is not known whether a rapid and immediate reactive vasospasm occurs directly after SAH due to the multiple vasospastic mediators present in blood, platelets, and serum that completely surround the vessel adventitia after the hemorrhage in the place of normal cerebrospinal fluid (CSF). When cerebral angiograms are performed relatively soon (within a few hours) after the onset of SAH, approximately 10% reveal angiographic evidence of immediate vasospasm.\(^5,10\) These data suggest that an immediate reactive vasospasm occurs in a minority of SAH patients and implies a different mechanism for DCV. However, the later occurring DCV may in some way be linked to a transient immediate vasospasm.

The immediate morbidity from aneurysmal SAH is frequently secondary to increased intracranial pressure (ICP), as evidenced by the observation that 78% of SAH patients with acute symptomatic hydrocephalus improved after ventricular drainage.\(^11\) ICP elevation after SAH appears to result from subarachnoid blood that causes malfunction of the arachnoid villi through an acute blockage, preventing normal resorption of CSF.\(^12\) Additionally, because the blood leakage from the vessel at the time of the hemorrhage is directed into the CSF space at arterial pressure, the hemorrhage only stops after the local CSF pressure rises to arterial level. This high pressure precludes cerebral perfusion. The rapidity of restoration of cerebral perfusion dictates in many ways the resulting morbidity and mortality from the hemorrhage.
Clinical observations suggest that the cerebral vessels are still reactive during the initial time period after a SAH that precedes the onset of DCV. During this period, usually within 48 hours of the hemorrhage, most direct clip ligation treatments of berry aneurysms are performed. Some manipulation of the parent cerebral vessels is usually done during surgery and this often produces a direct visible vasospastic response of the vessels. This vasospastic response is apparent on the exteriors of the vessels and can be relieved by direct application of papaverine or similar agents that facilitate smooth muscle relaxation. This vascular reactivity clearly implies that the smooth muscle in the region of the SAH (where the later DCV will occur) functions relatively normally in the early period after the SAH.

Clinical symptoms of DCV usually appear between the fifth and twelfth days following the hemorrhage. Angiography performed during this time may reveal a diffuse constriction of major vessels, often including the internal carotid artery. It is presumed that smaller vessels including arterioles are equally or more constricted although they are more difficult to visualize via angiography. Vascular constriction may be only radiographically apparent (radiographic vasospasm) or also clinically apparent, often resulting in focal neurological signs or permanent deficits or infarcts. Various methods to diagnose DCV include transcranial Doppler to detect increased blood flow velocity, computed tomographic angiography (CTA), and direct cerebral angiography — at present the gold standard diagnostic test.

One of the clinical treatments shown to be most effective in prevention of DCV is early administration of the relatively specific cerebral smooth muscle calcium channel blocker, nimodipine. After DCV has begun, the mainstay of treatment is hyperdynamic therapy (enhanced blood volume and relative hypertension). This therapy promotes as much blood flow past the relatively constricted regions as possible by raising the pressure head in the systemic arteries leading to the brain. The most clinically effective treatment for severe vasospasm is therapeutic angioplasty. When possible, it is used to dilate proximal spastic vessels that may enhance blood flow into smaller arterioles that may also be involved.

Antifibrinolytic agents have been used to decrease rebleeding after aneurysmal SAH by preventing lysis of the blood clot tamponading the rent in the aneurysm. A meta-analysis of several trials of antifibrinolytic agents in SAH patients demonstrated that these agents significantly decrease the rebleeding rate. Unfortunately, they also significantly increase cerebral ischemia secondary to DCV, and therefore have no significant effect on outcomes compared to control patients. Failed trials of antifibrinolytic therapies in SAH patients confirm the importance of blood products in the subarachnoid space as critical in the pathogenesis of DCV. If blood products remain longer due to decreased lysis, then the DCV rate (along with secondary symptoms such as stroke and death) is considerably higher.

11.3 CRITICAL QUESTIONS ABOUT DCV

The clinical knowledge accumulated over many years raised a large number of questions about DCV and prompted multitudes of research studies of the human condition and animal models. Unfortunately, DCV is very difficult to duplicate in

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animal models for assessing the time course, histology, and other parameters of treatments. Research studies have partially answered several critical questions and the results will be discussed next.

11.3.1 Why Are Subarachnoid Arteries Susceptible to DCV?

It is unclear why cerebral arteries located in the subarachnoid space are susceptible to DCV. One hypothesis links interference in the nutrition of the intracerebral vessels to their susceptibility to vasospasm. Intracerebral vessels appear to lack the common nutrient-penetrating abilities present in other systemic arteries (vaso vasorum). Instead, it appears that pores or communication channels within the adventitia of intracerebral vessels allow access of CSF to the vessel media for critical glucose and nutrient supply. Thus, a thick coating of blood directly adjacent to the outer vessel wall after SAH may prevent nutrient access to the media and this eventually leads to media necrosis.

This does not appear to be a problem for the first few days after the SAH because the vessels remain externally reactive at operative exposure at least up to 72 hours after SAH. Eventually the lack of nutrient supply (combined with the enhanced tendency toward contraction due to the vasoconstrictive environment surrounding the vessel) leads to pathological changes within the vessel and at least partial necrosis of the media. Medial fibrosis and necrosis have been consistent findings in human specimens with symptomatic DCV.

Another hypothesis suggests DCV after SAH is due to vascular mitogens released by activated platelets inducing vascular cell proliferation in the arterial walls. Platelet-derived growth factor-AB is a powerful mitogenic growth factor for vascular smooth muscle cells and also promotes cell migration. Smooth muscle proliferation is stimulated within hours after injury and may increase wall thickness producing vessel stiffening that contributes to cerebral vasospasm. During the first week after SAH, it has been found that platelet-derived growth factor (PDGF) levels in the CSF of SAH patients are significantly higher than levels of nonSAH patients.

The time course of DCV is consistent with that of a cellular proliferation process (Figure 11.1). In animal models, immunohistochemical labeling using proliferating cell nuclear antigen (PCNA) shows smooth muscle replication in the vascular wall and significant changes in vascular mechanical properties. Consequently, in the days and weeks following SAH, small changes in arterial wall dimensions could theoretically thicken the vessel walls, which would dramatically decrease arterial compliance. Thus, vessel wall thickness may be a function of both media necrosis and smooth muscle proliferation, partly in response to the necrosis (to renew the vessel wall) and to mitogens readily available from blood products (Figure 11.1).

11.3.2 What Are the Likely Spasmogens Contributing to DCV?

It is well established that the proximity of dissolving blood in the subarachnoid space to the outer vessel wall leads to a large array of vasoactive substances that
maintain continuous contact with the outer surfaces of the blood vessels. It is postulated that the presence of these vasoactive substances around the walls of intracerebral vessels, which have at least partial wall necrosis, contributes to post-SAH DCV. Incubation of cerebral vessels in clotted blood followed by administration of blood products can lead to vasoconstriction. However, it has been difficult, however, to identify the spasmogen most responsible for DCV — the mechanism by which the effect occurs — and the linkage between short-term muscle contraction and the subsequent DCV.

Several agents have been hypothesized to be responsible for DCV, all of which are present in blood products, including serotonin, catecholamines, eicosanoids, and others. Convincing evidence suggests, however, that the vasoactive substance likely to be responsible for initiation of DCV is oxyhemoglobin. Oxyhemoglobin has several mechanisms of action that may be important in vasospasm including the release of free radicals, the initiation and propagation of lipid peroxidation, metabolism to the vasoactive substance bilirubin, release of eicosanoids and endothelin from the vessel walls, perivascular nerve damage, inhibition of endothelium-dependent relaxation, and induction of structural damage to the vessel wall. The precise role of these processes in the pathogenesis of DCV remains to be elucidated.

11.3.3 Why is the Onset of DCV Delayed?

With the combination of relative ischemia of the vessel wall due to lack of CSF nutrients and the intense vasoactive presence maintained against the outer arterial wall, eventually the arterial wall becomes thickened. A combination of necrotic smooth cells fills most of the media, together with proliferating smooth cell precurs-
sors, all leading to severe luminal narrowing. Instead of a vasospastic response at this time (5 to 7 days after the SAH), the vessel wall is thickened, has a small lumen, and cannot be dilated except with mechanical balloon pressure (angioplasty). What is not clear from previous pathologic studies is precisely when the mitotic turnover of smooth muscle cells begins to renew the damaged cells, and whether this smooth muscle cell proliferation is in response to the initial SAH, media necrosis, or earlier factors that appear prior to cell necrosis. A marker for mitosis could indicate when the SAH insult has led to the initial changes responsible for vessel necrosis and thickening.

One hypothesis is that smooth muscle cell turnover begins rapidly after the SAH insult, and reaches a peak after 5 to 7 days. However, the smooth muscle cells may require a more potent stimulus to begin mitotic activity, such as the later combination of relative ischemia and the mix of growth factors available from the blood coating the outer wall. The vessel thickening would then correspond to a combination of vessel necrosis of smooth muscle cells in the media and mitosis and hypertrophy of an underlying population of cells, which would lead to smooth muscle renewal and proliferation. The smooth muscle cell proliferation would presumably then proceed over days to a few weeks, leading to a repopulation of the media and resumption of normal vessel reactivity and caliber.

Thus, the time course of DCV is presumably delayed due to the slow onset of smooth muscle necrosis over several days. This, together with the combination of mitotic activity and hypertrophy of remaining cells, markedly increases the width of the media, leading to shrinkage of the vessel lumen. The 5-day period may be an unfortunate superimposition of these two processes of necrosis with associated cell swelling and the secondary hypertrophy and mitotic activity of smooth muscle cell turnover. This time period is compounded by the slow lysis of blood products by CSF and a correspondingly slow resumption of adequate vessel nutrition, presumably as CSF adventitial pores are reopened or reconstituted.

Cerebral vessels may show luminal narrowing for reasons other than media thickening and direct changes in smooth muscle cells. For example, there may be an infiltrative component suggestive of inflammation within the vessel wall in response to the SAH that may be separately treatable. The possible role of inflammation in vasospasm should be the focus of a search to determine the exact cellular content (other than smooth muscle precursor cells and mature or dying smooth muscle cells) within the thickened media. If inflammatory cells are specifically identified as significant components of thickened vessel walls, new therapeutic options for vasospasm may be developed in the future.

11.3.4 Why Does SAH Density Correlate with Risk of DCV?

The most probable explanation for the correlation of thickness of SAH on CT scans with the risk of DCV is that blood deposition adjacent to the vessel induces vascular wall necrosis by interfering with vessel nutrition and releasing spasmogens such as oxyhemoglobin. Theoretically, enhancing blood lysis in the CSF early after SAH
could lead to decreased risk of and faster recovery from DCV (but promote rebleeding if early aneurysm clipping is not performed). This approach is advocated by those attempting to treat vasospasm with infusion of urokinase or tissue plasminogen activator (tPA) into the subarachnoid space after SAH.

Several trials have demonstrated the potential benefits of intracisternal urokinase or tPA infusion after SAH in the reduction of DCV.\textsuperscript{34–37} These results led to a multicenter, randomized, blinded, placebo-controlled trial of intracisternally administered tPA in attempts to prevent DCV after aneurysmal SAH.\textsuperscript{38} Unfortunately, although the trial revealed a significant decrease in incidence of severe vasospasm in patients with thick subarachnoid clots treated with tPA, all other outcome measures, including overall incidence of angiographic vasospasm, incidence of clinical vasospasm, and outcome at 3 months were not significantly affected. Interestingly, overall bleeding complication rates did not increase with tPA. Although the benefits of tPA could potentially reach statistical significance in a larger trial, the results of this trial have dampened enthusiasm for fibrinolytic agents in SAH patients.

11.4 CAN ADVANCES IN SMOOTH MUSCLE CELL BIOLOGY FACILITATE UNDERSTANDING?

Cerebral blood vessels are composed primarily of smooth muscle cells (long, tapering, single nuclei cells with thick-to-thin filaments aligned with the long axis) within the media. Smooth muscle contraction is involuntarily triggered by the autonomic system or by hormones, and is designed for slow, long-lasting contraction. Smooth muscle cells are specifically designed to maintain tension for prolonged periods (passive maintenance) while hydrolyzing five- to tenfold less ATP than skeletal muscle cells performing the same task. Like other muscle cells, contraction occurs because of myosin and actin. The actin in smooth muscle cells has a different amino acid sequence than that of cardiac or skeletal muscle cells, but there appears to be no known functional significance.

Smooth muscle myosin resembles skeletal myosin; functionally, the level of ATPase activity is tenfold lower, which allows more direct calcium regulation of contraction. Also, smooth muscle myosin can interact with actin filaments and cause contraction only when its light chains are phosphorylated. When the myosin is dephosphorylated, it cannot interact with actin and the muscle relaxes. Specific enzymes accomplish this calcium-dependent phosphorylation and dephosphorylation of the myosin light chain.

Arteries have thick walls of connective tissue and vascular smooth muscle cells (VSMCs) lined by monolayers of endothelial cells. The endothelial cells are separated from the smooth muscle cells by a basal lamina and then the elastic fibers of the internal elastic lamina. The arterial wall morphology can change by both smooth muscle hypertrophy and hyperplasia. Hypertrophy occurs by adding cytoplasmic elements, but is reversible because the cells enlarge without changes in DNA. Unlike skeletal and cardiac muscle, smooth muscle can divide and may recruit undifferentiated cells (pericytes) to become smooth muscle cells. This mitotic behavior is stimulated by various growth factors.
The predominant growth regulators of VSMCs and pericytes are fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs), transforming growth factor-beta 1 (TGF-β1), and epidermal growth factor (EGF). When stimulated by any of these growth factors at appropriate concentrations, VSMCs can begin execution of the mitosis program within hours. For vascular smooth muscle cells, PDGF-BB precipitates the greatest degree of growth, with PDGF-AA stimulating small but significant growth, and PDGF-AB causing an intermediate amount of growth.

PDGF-AB is the predominant form of growth factor released from activated platelets. Depending on dose, TGF-β1 is inhibitory to SMCs but not to pericytes. Both acidic and basic FGFs are strong mitogens to pericytes and SMC proliferation.39 Also, tumor necrosis factor-alpha (TNF-α), a ubiquitous cytokine involved in inflammatory states, has been reported to stimulate SMC growth in culture. TNF receptor activation is known to induce SMC apoptosis more in rapidly proliferating neointimal cells than in more slowly replicating medial cells.40

Although SMC proliferation likely occurs as part of the media replacement during and after DCV, little direct evidence for this has been shown in human arterial samples to this point. However, multiple mitogens leading to such proliferation are clearly present in the SAH mix around cerebral vessel walls and other factors, such as hypoxia, can induce mitogens.

11.5 SUGGESTED RESEARCH AVENUES AND TREATMENT OPTIONS

The development of a suitable model system for the study of DCV has been difficult. In general, three types of model systems have been used to investigate cerebral vasospasm: cell culture, isolated cerebral vessels, and whole animals. Whole animal models of vasospasm range from intracisternal injection of autologous blood to craniotomy for exposure of cerebral arteries and direct application of blood clot to their surfaces.41,42 Although the craniotomy model replicates well the human disease process and even its response to nimodipine,43 it involves primates that are very expensive and ethically troubling, and the model itself is technically difficult.

Less challenging and expensive in vitro models of DCV have used isolated cerebral vessels or cultured cells. The difficulty with isolated cerebral vessels is that they survive at best only a few days in culture, and are only beneficial in the study of early immediate vasospasm rather than the entire DCV process.44,45 Interestingly, SMC isolated from rat aortas and exposed to hemoglobin in vitro have been found to develop changes similar to those seen in DCV, suggesting that some mechanistic features of the disease process may be investigated in cell culture systems.46 Of course, the ability to study pharmacologic and other therapies in a vessel-free system is limited.

An alternative experimental approach is available as a result of the recent development of the ability to grow blood vessels entirely in vitro.47,48 This system has the advantage of allowing in vitro study of vessels of the size desired and over a longer period than isolated vessels are able to survive. Additionally, since the growth media
can be changed as desired, these model vessels offer a novel way to investigate changes in the vascular SMC on a detailed time schedule in an ischemic or vasoconstrictive environment.

Treatment options can also be directly demonstrated in this model because it allows easy access to both the luminal and adventitial sides of the vessel. In many ways, these vessels grown in vitro are similar to human cerebral vessels. They are of the same size (a few millimeters) and both lack vaso vasorum or nutrient feeding vessels to the media. The in vitro cultured vessels are surrounded by a culture growth medium that can be altered to be like CSF, and then the vessels can be deprived of substrates or surrounded by blood to imitate in many ways the SAH process that underlies DCV.

Unfortunately, short of animal models that fully duplicate the sequence of events present in the human situation, further human tissue may be the most valuable study source and clearly the most valid in terms of predicting human treatment. Studies focusing on muscle cell turnover and mitotic activity in human specimens will be critical for mapping out the full sequence of events of DCV beyond the limits of ordinary pathological examination. This type of analysis could include assessing proliferation of smooth muscle cell precursors, hypertrophy, mitotic activity, and in particular assessing the relative contributions to the media enlargement of SMC necrosis, SMC hypertrophy, and inflammation.

Further treatment efforts could be directed at early or late phase. Early intervention could be performed to enhance CSF lysis of blood products in an effort to restore appropriate nutrition levels to the media. If an early proliferative phase exists and if it can be safely slowed or postponed to await the resolution of necrosis, less reduction of the vessel caliber may occur. The danger of slowing down reactive smooth muscle changes is that SMC growth may be insufficient by the time of resolution of the necrosis for vessel strength, which could lead to spontaneous vessel necrosis and possibly rupture. Other interventions may reduce necrosis or enhance tolerance of SMC to the relative ischemic conditions present after SAH. Thus, preventing or delaying necrosis may obviate the need for delayed SMC proliferation.

Many ischemic effects observed in clinical DCV are results of vasospasm in small vessels that are not amenable to current vascular interventional treatment (therapeutic angioplasty). Thus, further systemic or local medical treatment may be very helpful for treating or forestalling cerebral ischemic changes observed in DCV. Vasospasm has been most intensively studied in larger vessels, but the pathogenesis in small vessels (i.e., arterioles) may differ due to the different mixtures of vessel wall components compared to the larger more proximal vessels. Thus, an in vitro model that duplicates some features of small vessels may also be of significance. The smaller arterioles share many features of the larger cerebral vessels, in that vaso vasorum is also absent and the vessels are also located within the subarachnoid space, susceptible to SAH and its secondary effects.

11.6 CONCLUSIONS

DCV is a complex and time-dependent phenomenon that is not completely understood, partly due to the lack of a suitable experimental model that clearly reproduces
the changes observed in human vessels in DCV. Further, more effective clinical treatments will likely come from enhanced understanding of the pathophysiology of the disease, particularly the biology of smooth muscle cells because the majority of empiric treatments over the past 30 years have not demonstrated substantial efficacy.

Short-term animal models of DCV seem to have little relevance or validity — a conclusion echoed in 1985 by Wellum et al. Thus, development of new animal models and understanding mechanisms involved in both necrosis and proliferation may be the key to future translational treatments.

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