Vasospasm as the sole cause of cerebral ischemia: how strong is the evidence?

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✓The authors review literature that challenges the view that vasospasm involving large arteries is the exclusive cause of delayed ischemic neurological deficits (DINDs) following subarachnoid hemorrhage. They discuss alternative mechanisms and review the evidence supporting a potential role for thromboembolism. They conclude that vasospasm and thromboembolism play interrelated and additive roles in the development of DINDs, and that this interaction provides opportunities for novel therapeutic approaches.

KEY WORDS • cerebral vasospasm • subarachnoid hemorrhage • thromboembolism

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.—Karl Popper

EARLY observations of the cortical surface revealed that electrical, chemical, and mechanical stimuli often caused arterial constriction.^{33,86,106} Echlin²² demonstrated in 1942 that this induced vasospasm could in turn impair CBF. In 1949, Robertson⁹⁹ investigated cerebral infarction after SAH, and was the first to speculate on arterial spasm as a possible cause. Soon thereafter, a small study of patients with SAH was published in which vasospasm was demonstrated angiographically,²³ and the connection between vasospasm and ischemia after SAH was established.

In subsequent studies, researchers confirmed that angiographically demonstrated vasospasm is quite common after aneurysm rupture and is frequently associated with clinical evidence of cerebral ischemia.^{5,117} In 1965, Kagstrom, et al.,⁵⁴ demonstrated that vasospasm is usually “delayed” for at least 3 days after the initial SAH. Other investigators have elaborated on the association and temporal relationship between angiographically demonstrated and “clinical” vasospasm.^{31,38,65,79} Considerable effort over the years has gone into clarifying the pathogenesis, clinicopathological associations, and treatment of vasospasm. A recent MEDLINE search revealed that since 1953 more than 38,000 scientific articles that address one or more aspects of cerebral vasospasm have been published. This research has established a strong association between angiographically demonstrated and clinically apparent vasospasm.

Abbreviations used in this paper: CBF = cerebral blood flow; DINDs = delayed ischemic neurological deficits; MR = magnetic resonance; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury; TCD = transcranial Doppler.

Evidence Against Vasospasm

Several lines of evidence cast doubt on angiographically confirmed vasospasm as the sole cause of DINDs. These include the following: 1) the relatively limited role that large arteries play in control of CBF; 2) a lack of correspondence between the sites and severity of angiographically confirmed vasospasm and cerebral ischemia; 3) the appearance of cerebral infarcts at autopsy; and 4) the disappointing clinical effects of vasospasm therapy.

First, although large cerebral arteries contribute more to vascular resistance than do arteries elsewhere in the body, their contribution to the regulation of CBF is still relatively minor.^{29,41} Many proponents of large-vessel vasospasm have referred to the Hagen–Poiseuille equation, in which flow varies based on the fourth power of a vessel’s radius. However, the equation was designed for large-diameter rigid tubes carrying newtonian fluids, and there is experimental evidence that it correlates poorly with blood flow, even in the absence of distal autoregulation.^{1,90} Marked constriction of large cerebral arteries can occur without a decrease in parenchymal CBF.²⁸

Second, there is poor correlation between the sites and severity of angiographically confirmed vasospasm and either symptomatic^{2,99} or measured^{35,81} cerebral ischemia. Symptoms and findings of DINDs often follow peak vasospasm by several days. The presence and location of angiographically demonstrated vasospasm fails to correlate with areas of cerebral infarction in as many as one third of cases.⁹⁶ There are cases in which documented SAH-induced ischemia occurs without vasospasm,^{25,35,72} and it is possible to increase CBF in experimental vasospasm without reversing the spasm itself.^{66,89} Minhas, et al.,⁷⁴ performed simultaneous positron emission tomography and TCD ultrasonography studies in patients after SAH. They did not observe a correlation between the two, thereby “calling into question the traditional concept of large-vessel vasospasm.”

Third, autopsy studies performed in patients after SAH reveal that the majority of infarcts are widespread and scattered, small, wedge-shaped, or laminar.^{78,115,116} This pattern is more consistent with small thromboemboli than with large arterial spasms. Stoltenberg-Didinger,¹¹⁵ who studied 156 patients who died and had not undergone surgery, found that 76% had evidence of small infarcts. In contrast, fewer than 6% had large, territorial lesions.¹¹⁶ These small infarcts were often located immediately beneath the thickest subarachnoid clots. These findings and others prompted Neil-Dwyer and colleagues⁷⁸ to suggest diffuse microangiopathy as the major cause of DINDs after aneurysmal SAH.

Fourth, in clinical practice there are several effective therapies that are used to combat angiographically demonstrated vasospasm. However, these treatments had less of an effect on infarct burden or patient outcome.^{46,56,69,70,97} Treatments such as hypertension, hypervolemia, and hemodilution (known as triple-H therapy)¹²⁴ or intracisternal implantation of nicardipine pellets after SAH⁵⁸ can reduce angiographically confirmed vasospasm but do not affect DINDs. In some studies investigators suggest that endovascular treatment of aneurysms is associated with less frequent and less severe angiographically demonstrated vasospasm than surgical occlusion. However, this has occurred without a corresponding improvement in outcome.⁹⁷ Finally, transluminal angioplasty and intraarterial papaverine administration are effective in reversing angiographically demonstrated vasospasm. Nevertheless, their effect on patient outcome is less certain.^{91,132}

Alternative Theories

In 1988, Mendelow⁷³ cautioned against equating vasospasm with DINDs and offered several alternative causes of the latter. Some causes of ischemia, such as mechanical arterial compression by brain displacement, parenchymal masses, rebleeding of hemorrhages, or hydrocephalus usually can be excluded using modern neuroimaging techniques. Other causes, such as hypovolemia, hypotension, and dehydration are uncommon because they are actively managed by present-day medical therapy. Other hypotheses to explain DINDs deserve further consideration. These potential causes include small-artery spasm, thromboembolic events, direct toxic effects of the SAH, or some other delayed effect of the global ischemic insult that occurred at the time of aneurysm rupture.

It is not unreasonable to expect that arterioles too small to be visualized using arteriography ($< 100\text{-}\mu\text{m}$ diameter) react to SAH as do large vessels. Arteriolar constriction may occur directly in response to blood or as a conducted vasomotor response.^{18,105} There is evidence, however, that the small arterioles mainly responsible for control of CBF may not respond to SAH as do larger arteries. Although oxyhemoglobin causes modest cerebral arteriolar constriction,^{42,55,121} there is a pial barrier that protects parenchymal vessels from exposure to subarachnoid blood and large particles.^{49,63} Surface arteries, even small ones, can constrict without decreasing CBF to the underlying cortex.^{113,122} Furthermore, exposure to blood does not cause vasospasm of small parenchymal arterioles, either in vivo or in vitro.^{87,129}

An alternative explanation for DINDs is the possibility that blood or its breakdown products are directly neurotoxic. There is evidence in studies of TBI and intracerebral hemorrhage that supports this contention. Nevertheless, in animal models of SAH^{4,17,93,94} and models that involve exposure to blood products,¹⁹ ischemia invariably precedes necrosis.

Early after aneurysm rupture, CBF and cerebral metabolism are impaired.^{14,52,60} Based on TCD studies obtained soon after hemorrhage, Miranda and associates⁷⁵ recently reported their findings that early signs of cerebral ischemia detected using TCD ultrasonography are more common than previously suspected. They hypothesize that early ischemia results from elevated intracranial pressure and contributes to DINDs through mechanisms that have not yet been determined.

The Case for Thromboembolism

Thromboembolism can result from activation of tissue thromboplastin or from endothelial injury, and the two prothrombotic mechanisms reinforce each other.¹²⁶ The brain has the body's highest concentrations of tissue thromboplastin, or tissue factor,^{37,95} much of it localized in the adventitia of cerebral arteries³² and perivascular astrocytes.²⁴ There is considerable evidence that tissue factor in the arterial walls plays a major role in thrombosis.¹⁵ When activated, the tissue factor coagulation pathway assembles thrombin complexes on the pericytic membranes to cause intravascular thrombosis.¹⁰ In TBI, this appears to be a focal form of disseminated intravascular coagulation.^{47,114} Aneurysm rupture is rapidly followed by activation of both platelets and coagulation. If severe enough, this stimulated coagulation activity consumes many clotting factors and results in coagulopathy. Markers of hypercoagulation, factor consumption,^{6,64} and platelet activation^{9,43} appear soon after the hemorrhage. When compared with systemic levels, the values of these markers are always higher in the cerebrospinal fluid^{59,119} and jugular venous blood,^{16,44} suggesting their cerebral origin. Severe or prolonged elevation of these various markers is usually associated with more severe DINDs.^{50,64} For example, in one recent report of almost 400 consecutive patients with SAH, low platelet counts were linked to DINDs, small hypodensities on computed tomography scans, and worse clinical outcome.⁴⁵ Although the authors attributed these changes to heparin-induced thrombocytopenia Type II, they did not confirm the diagnosis with laboratory tests in most cases and did not comment on other coagulation parameters.

Subarachnoid hemorrhage also causes considerable injury to the vascular endothelium,^{30,51} resulting in desquamation.^{87,133} This is accompanied by the appearance of markers of endothelial activation in blood, cerebral dialysate, and cerebrospinal fluid;^{34,57} blood-brain barrier dysfunction;^{108,133} and platelet accumulation.^{13,30} The fate of microthrombi created by either mechanism depends on vessel size. In larger arteries, microclots are likely to embolize. Small arterioles would be more liable to thrombose. Several investigators have demonstrated that microemboli can indeed cause cerebral infarction and symptomatic ischemia in animals and humans.^{8,98}

Evidence for vasospasm as the sole cause of cerebral ischemia

Platelet aggregation¹⁰⁷ and isolated thromboemboli have been noted after SAH in the cortical arteries of experimental animals^{30,84} and in patients at autopsy.^{76,120} Consistent with these findings, TCD measurements detected microembolic signals in many patients with ruptured aneurysms, even in areas in which there was no proximal vasospasm.^{36,62,100} Romano and coworkers¹⁰⁰ performed TCD monitoring of the middle cerebral artery for 30 minutes three times a week during the intensive care unit stay of 23 patients with ruptured aneurysms. Microembolic signals were detected in 70% of the patients and 32% of the insonated vessels. These findings support the suggestion that a large number of emboli, some of which may be causing symptomatic cerebral infarctions, occur after SAH.

Similarly, routine computed tomography and MR imaging studies obtained in patients with SAH have documented a 44 to 67% incidence of multiple small infarcts.^{20,36,39,48,53,85,92,110} Furthermore, there is a strong association between the number of microembolic signals and the presence of DINDs in most series. Rordorf and coworkers¹⁰⁴ studied six patients with combined diffusion and perfusion MR images. They confirmed widespread ischemic lesions, surrounded by areas of reduced CBF. Direct evidence to support a role for thromboembolic phenomena in DINDs was described by Peltonen, et al.,⁸⁵ who found a positive correlation between coagulopathy after aneurysm rupture and the later appearance of infarcts.

Parallel Mechanisms

We believe that two or more of the potential mechanisms causing DINDs may interact to worsen the eventual ischemic state after SAH. Indeed, the combination of vasospasm and thromboembolism has the capability to create far greater damage than either mechanism alone. This has been confirmed in studies of carotid artery stent placement, in which it has been suggested that the combination of microemboli and impaired CBF produces more damage than either one alone.⁸²

Several converging lines of evidence from pharmacological studies support roles for both inflammation and coagulation in the pathogenesis of DINDs after aneurysmal SAH. For example, many treatments that prevent or ameliorate DINDs also have anticoagulant effects. Protease inhibitors, which can prevent cerebral vasospasm, also inhibit clotting factors.^{11,130,131} Aspirin and other nonsteroidal antiinflammatory drugs, which also have antiplatelet and anticoagulant effects, have been found by some investigators to protect against vascular spasm and DINDs.^{48,123} Nimodipine, which reduces the incidence of DINDs, does not prevent vasospasm.^{88,109} Perhaps its fibrinolytic¹⁰¹ or antiplatelet⁸⁰ properties account for its success. Statins protect against DINDs^{26,83} and also reduce microclot formation after TBI.⁷¹

It is well known that many effective antiinflammatory agents also have antiplatelet and anticoagulant properties.^{12,125} This is also true of endothelin antagonists, which can attenuate experimental vasospasm.^{127,128} It must be remembered that coagulation is an integral part of the inflammatory reaction; the two processes are mutually reinforcing.^{27,68} Inflammatory mediators also activate inter-cellular and vascular adhesion molecules, which recently have been shown

to play important roles in vasospasm.⁶¹ These same adhesion molecules promote platelet thrombi. Because of extensive overlap, mechanisms of inflammation and blood coagulation are mutually reinforcing after SAH.^{21,94}

Hemodilution treatment, to the extent that it prevents DINDs, also inhibits blood coagulation. Early lysis of subarachnoid clots with intracisternal tissue plasminogen activator shows promise in preventing vasospasm and DINDs.⁷ Its protective effect may also arise by promoting lysis of intravascular thromboemboli. Interestingly, one study of intrathecal urokinase revealed a more striking effect on DINDs than on vasospasm, from which it was inferred that the two might have different mechanisms.⁴⁰ The association of antifibrinolytic therapy (which was popular in the 1970s) with vasospasm and DINDs is well documented.¹⁰² Recently there has been some interest in reviving this treatment as a short-term means of preventing aneurysm rebleeding.^{67,77,118} If our contention is correct, this practice is potentially hazardous. Finally, in a number of recent reports investigators have noted a high incidence (20–60%) of small infarcts detected using MR images obtained after coil occlusion of ruptured cerebral aneurysms.^{3,62,103,112} This is considered by most to be a complication of endovascular therapy, although the infarct could have arisen just as easily from spontaneous thromboemboli. The finding that follow-up imaging frequently reveals new lesions proximal to the treated aneurysms¹¹¹ is consistent with a role for thromboembolism in the process.

Conclusions

We propose that thromboembolism is a mechanism that parallels and complements vasospasm in producing DINDs. The association of both coagulopathy and microembolic signals on the one hand with radiographic and clinical evidence of DINDs on the other suggest several important clinical applications. Activation of coagulation appears early after SAH and may allow early identification of the patients at greatest risk. The mechanisms of thromboembolism bring to mind a number of therapeutic agents with the potential to avert or ameliorate DINDs. These include antithrombotic and novel fibrinolytic agents, both of which can retard new clot formation without endangering the clot securing the aneurysm.

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