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Spreading Depolarization:

A Possible New Culprit in the Delayed Cerebral Ischemia of Subarachnoid Hemorrhage

Dr. Lewis Z. Leng, MD, **Dr. Matthew E. Fink, MD**, and **Dr. Costantino Iadecola, MD**
Departments of Neurological Surgery (Dr Leng) and Neurology and Neuroscience (Drs Fink and Iadecola), and Division of Neurobiology (Dr Iadecola), Weill Cornell Medical College, New York Presbyterian Hospital, New York, New York

Abstract

A neurysmal subarachnoid hemorrhage (SAH) is a devastating disease with a high mortality and morbidity rate. Gradual improvements have been made in the reduction of mortality rates associated with the disease during the last 30 years. However, delayed cerebral ischemia (DCI), the major delayed complication of SAH, remains a significant contributor to mortality and morbidity despite substantial research and clinical efforts. During the last several years, the predominant role of cerebral vasospasm, the long-accepted etiologic factor behind DCI, has been questioned. It is now becoming increasingly clear that the pathophysiology underlying DCI is multifactorial. Cortical spreading depression is emerging as a likely factor in this complex web of pathologic changes after SAH. Understanding its role after SAH and its relationship with the other pathologic processes such as vasospasm, microcirculatory dysfunction, and microemboli will be vital to the development of new therapeutic approaches to reduce DCI and improve the clinical outcome of the disease.

Spontaneous subarachnoid hemorrhage (SAH) accounts for 5% of strokes and affects more than 30 000 people per year in the United States.[1] It is associated with a high mortality rate of up to 67%, and only half of the survivors are able to live independently.[2] Because those affected are typically between 40 and 60 years of age and many survivors require assistance with activities of daily living, SAH results in a tremendous burden to society in terms of lost productivity and resources used.[3] With advances in rapid diagnosis such as computed tomographic (CT) angiography, improved neurointensive care, and emerging endovascular technologies, a decrease in mortality rates after SAH has been noted in the last 30 years.[2] However, SAH remains one of the most devastating and difficult-to-treat neurological diseases.

Correspondence: Costantino Iadecola, MD, Division of Neurobiology, Weill Cornell Medical College, 407 East 61st St, Rm RR303, New York, NY 10065 (coi2001@med.cornell.edu).

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Subarachnoid hemorrhage usually results from the rupture of a saccular intracranial aneurysm. The extravasation of blood into the subarachnoid space produces characteristic patterns of hemorrhage in the basal cisterns of the brain. With the initial rupture, individuals experience a severe headache, nausea, vomiting, loss of consciousness, cranial nerve deficits, sensorimotor deficits, and seizures. The severity of the initial bleed remains a major determinant of outcome after SAH.[1] Individuals fortunate enough to survive the initial hemorrhage and early complications such as hydrocephalus, respiratory failure, and rebleeding face the significant risk of developing delayed cerebral ischemia (DCI). Delayed cerebral ischemia typically occurs between 3 and 14 days after the initial bleed[1] and clinically manifests as a change in level of alertness and/or new focal neurologic deficits.[4] Delayed cerebral ischemia may progress to cerebral infarction, leading to permanent neurologic deficits, disability, and death. In fact, this delayed complication is the most important cause of morbidity and mortality for survivors of the original hemorrhage that have had their aneurysm effectively secured.[5] Delayed cerebral ischemia has traditionally been ascribed to cerebral vasospasm, a narrowing of large and medium-sized cerebral arteries that is caused by the subarachnoid blood. However, in recent years, the primary role of vasospasm in the pathophysiology of DCI has been increasingly challenged,[6–9] shifting the emphasis toward alternative mechanisms. In this article, we will briefly review the mechanisms of DCI, focusing on recent provocative findings that implicate recurrent waves of cortical spreading depression (CSD) in the pathophysiology.[10] A more comprehensive review of the causes of SAH-induced brain injury and its complications can be found in several excellent recent publications.[1,6,9]

ROLE OF VASOSPASM

The role of vasospasm in DCI has become so firmly entrenched that the terms *symptomatic vasospasm* and *delayed ischemic neurologic deficits* are often used interchangeably.[11] Since vasospasm was first linked to DCI in the 1940s,[12] considerable effort has been invested in attempting to understand the etiology of vasospasm and breaking the chain of events leading to DCI. However, in pursuit of this goal, evidence has slowly accumulated that questions the role of vasospasm as the sole factor in the pathogenesis of DCI. The case against a primary causative role of vasospasm in DCI includes (1) the imperfect link between major vessel cerebral vasospasm, clinical symptoms of DCI, and outcome, (2) the inconsistent temporal and spatial relationship between angiographic vasospasm and DCI, (3) the inconsistent cerebral blood flow (CBF) changes associated with vasospasm, and (4) the conflicting and disappointing results of antivasospasm therapies. These points are discussed in greater detail.

Vasospasm and Clinical Outcome

Despite the fact that angiographic vasospasm is detected in up to 70% of cases after SAH, only 20% to 40% of patients are symptomatic.[6] No standardized definition has been adopted but symptomatic vasospasm has been typically defined as a deterioration in neurologic status after other causes have been ruled out including hydrocephalus, seizures, cerebral edema, metabolic derangements, drugs, and infection. A recent study by Frontera et al[11] highlighted the discrepancy between angiographic vasospasm and clinical outcome. The

investigators tracked the outcome of patients with SAH based on the occurrence of angiographic vasospasm, vasospasm by transcranial Doppler (TCD) criteria, symptomatic vasospasm, and DCI. In this study, DCI was specifically defined as symptomatic vasospasm or a new infarct on imaging that was attributable to vasospasm. Of those patients with angiographic vasospasm, only 34% had neurologic decline that could be considered symptomatic vasospasm and only 41% had neurologic decline or a new infarct on imaging that could be attributed to vasospasm. Furthermore, neither angiographic or TCD vasospasm were associated with worse clinical outcome measures. Delayed cerebral ischemia and symptomatic vasospasm were associated with worse activities of daily living, cognitive impairment, and quality of life measures at follow-up. Only DCI was associated with increased death and severe disability.

Temporal and Spatial Relationships

Vasospasm and DCI are poorly related temporally because the symptoms of DCI commonly occur several days after vasospasm reaches its peak.[6,7] The inconsistent spatial correlation between vasospasm and DCI has been demonstrated in multiple studies. Rabinstein et al[13] found that the presence of angiographic or TCD vasospasm had a positive predictive value and negative predictive value for the occurrence of cerebral infarction of only 67% and 72%, respectively. Notably, in only 67% of cases was the infarct location correctly predicted by the location of angiographic vasospasm. In a study that used CT perfusion and CT angiography to evaluate vasospasm and ischemia after SAH, the most hypoperfused area failed to correlate with the most vasospastic vessel in 35% of the cases.[14] Moreover, only 57% of patients with severe vasospasm had DCI and 21% of patients without vasospasm still developed DCI. The spatial discrepancy between vasospasm and DCI has also been observed in studies using conventional angiography and CT.[15] Finally, it is well documented that delayed infarcts can occur without evidence of vasospasm.[15]

Vasospasm and Ischemia

Are the effects of vasospasm on CBF sufficient to cause ischemia and infarct? In CT perfusion studies after SAH, CBF in areas supplied by vessels with vasospasm ranged from 26.4 to 41.5 mL/100 g/min.[14,16,17] This range of CBF values is above the assumed threshold for ischemic injury, ie, 25 mL/100 g/min.[18] The findings with CT perfusion have been corroborated by studies that used more reliable methods to measure CBF. Jost et al[19] used positron emission tomography to quantitate CBF and observed that areas with vasospasm had a CBF of 36.7 mL/100 g/min vs 44.5 mL/100 g/min in areas without vasospasm. Furthermore, in several studies that used TCD criteria for vasospasm and either positron emission tomography or xenon-CT to measure regional CBF, no correlation was found between vasospasm assessed by TCD and reduced CBF.[20,21]

Clinical Trials

The outcome of trials for therapeutics directed at reversing vasospasm has been less than satisfactory. The mainstay of vasospasm treatment after SAH has been triple-H therapy (hemodilution, hypervolemia, and hypertension). First, it is unclear whether triple-H therapy has beneficial effects on CBF. In a recent review by Dankbaar et al,[22] only hypertensive therapy demonstrated more consistent positive effects on CBF. In terms of clinical outcome,

there is even a greater paucity of comparative trials studying triple-H therapy or any of its components. In a randomized controlled trial of hypervolemia by Lennihan et al,[23] no difference in mean global CBF as measured by xenon-CT or clinical outcome at 3 months was detected. A small randomized controlled trial of prophylactic hypervolemia and hypertensive therapy found no difference in TCD vasospasm, clinical vasospasm, perfusion on SPECT, or clinical outcome at 1 year.[24] A retrospective review of patients with SAH with symptomatic vasospasm who were treated with an algorithm of hypervolemia and hypertensive therapy showed that clinical responders to therapy did not show improvements in activities of daily living or cognitive function and had the same cerebral infarction rate as those who did not respond to therapy.[25] The emerging second line of treatment for vasospasm has become endovascular interventions. Angioplasty and intra-arterially delivered vasodilators such as papaverine and verapamil have shown the ability to reverse angiographic vasospasm.[1] However, there is no definitive evidence that the interventions have improved outcomes.[26] A randomized study of prophylactic balloon angioplasty in patients with SAH with Fisher scale III hemorrhages demonstrated no difference in clinical outcomes between the treatment and control groups.[27] To date, the 1 drug that has consistently decreased the risk of death, disability, and delayed ischemia after SAH is nimodipine.[28] Initially thought to target vasospasm and therefore prevent DCI, it has subsequently been shown to have no effect on the development of vasospasm after SAH.[29] Interestingly, nicardipine, another calcium channel blocker, appears to reduce vasospasm but has no effect on clinical outcome.[28,29] Most recently, attention has been directed toward endothelin, a potent endogenous vasoconstrictor and has been implicated in the pathogenesis of vasospasm. In experimental models of SAH, endothelin receptor antagonists demonstrated the ability to reduce vasospasm.[30] Although an initial trial with a non-selective endothelin receptor antagonist demonstrated no difference in cerebral infarction rates or clinical outcomes,[31] it was suggested that the lack of effect could result from inhibition of both endothelin A and endothelin B receptors, which have opposing effects on vascular tone, endothelin A mediating vasoconstrictor and endothelin B vasodilatation. Therefore, it was hypothesized that a selective endothelin A receptor antagonist may have a benefit. Two trials were conducted using the endothelin A receptor antagonist clazosentan. The preliminary phase 2a study[32] demonstrated reduction of angiographic vasospasm. In the follow-up CONSCIOUS-1 study,[33] which involved 413 patients, a dose-dependent reduction of angiographic vasospasm was observed. In the highest-dose group, there was a 65% relative risk reduction of vasospasm. Despite this impressive efficacy in ameliorating vasospasm, no significant difference in mortality or morbidity was shown. Thus, effective reversal of vasospasm did not translate into reduction of DCI-related mortality or morbidity and brings to question the primary role of vasospasm in the development of DCI.

THE QUEST FOR ALTERNATIVE MECHANISMS

These therapeutic failures and the other lines of evidence reviewed above have shifted the attention to alternative mechanisms for DCI including microcirculatory spasm, microthrombosis, and cortical spreading depression. Histopathological studies have demonstrated luminal narrowing of intraparenchymal arteries and arterioles after experimental SAH.[34] Some of these findings have been correlated in human studies but the

exact clinical relevance of microcirculatory dysfunction, sometimes termed *distal vasospasm*, in the development of DCI remains unclear.[35] After SAH, platelet activation, platelet aggregation, and activation of the coagulation cascade are noted, which has led to the suggestion of a possible role of microthrombosis and thromboembolism in DCI.[6] This has been corroborated by ultrasonography studies that noted high incidence of emboli in patients with SAH and an association with DCI.[36] An autopsy study by Stein et al[37] found that cerebral micro-clot burden had a strong association with DCI. Furthermore, microclot burden had 2 temporal peaks. An initial peak occurred within the first 2 days after SAH and a second peak appeared at the end of the first week through the second week, which correlates temporally with the onset of DCI. Despite these lines of evidence, antiplatelet and anticoagulation therapeutics have not been demonstrated to improve the outcome of SAH.[6] The recent demonstration that SAH is associated with waves of CSD has revealed yet another potential mechanism for DCI, which is discussed in detail in the next section.

THE CASE FOR CORTICAL SPREADING DEPRESSION

Cortical spreading depression was first described in rabbit cerebral cortex by Leão in 1944.[38] It is a self-propagating wave of neuronal and glial depolarization that travels at a characteristic 2 to 5 mm/min and can be triggered by a variety of stimuli.[39] The mass depolarization of cells results in a redistribution of ions and neurotransmitters, including an increase in extracellular potassium ions and glutamate, which can set off additional depolarizations, leading to a cycle that ends in neuronal inactivation.[39] Electrocorticographically, this is observed as a period of transient depression in cortical electrical activity, hence the term CSD. To re-establish the ionic gradients, sodium and calcium pumps are activated to reverse the massive cation influx.[40] To provide the energy substrates to fuel the ionic pumps driving neuronal repolarization, CSD, in the normal brain, is associated with an increase in regional CBF and oxygen delivery.[39] However, after brain damage, the hyperemia coupled with CSD is reversed into a reduction of CBF that travels with the depolarization wave (spreading ischemia).[41,42] In animal models, various pathologic conditions such as hypoxia, hypotension, transient ischemia from microemboli, low glucose level, high extracellular potassium ion concentrations, nitric oxide depletion, and free hemoglobin have been demonstrated to trigger CSD with spreading ischemia.[43–46] The combination of decreased CBF and increased energy requirements imposed by CSD may worsen neuronal injury.[42] In support of this hypothesis, neocortical application of a solution containing hemoglobin with high potassium ion or low glucose level triggered CSD and spreading ischemia, leading to cortical infarction.[43]

Cortical spreading depression has long been hypothesized to be the physiologic correlate of migraine auras[47] but, until recently, it was not definitely known whether CSDs occur in the human brain under pathologic conditions such as ischemia. During the past few years, several studies using subdural electrode strips have confirmed the presence of CSD in the human cortex after thromboembolic stroke, traumatic brain injury, spontaneous intraparenchymal hemorrhage, and SAH.[10,48–50] To elucidate the role of CSD in SAH and DCI, Dreier et al[10] performed simultaneous laser Doppler flowmetry for CBF measurement and electrocorticography in a group 13 patients with SAH. To this end, a single subdural strip embedded with recording electrodes and optodes for CBF measurement was implanted

in patients with SAH who had aneurysm clipping. In a select group of patients, an oxygen probe was also inserted into the adjacent brain to record tissue partial pressure of oxygen. Despite sampling only a limited area of the cortex, isolated CSDs were detected in 12 of 13 patients. These CSDs were associated with either an increase or a decrease in CBF. In cases in which the oxygen sensor was present, hyperemic CSDs led to brain hyperoxia, whereas oligemic CSDs were associated with hypoxia. In 5 patients, clusters of recurring CSDs were measured that were consistently associated with hypoperfusion. The clusters resulted in depression of cortical activity for 2 to 3 hours and, in 1 case, up to 60 hours. The hypoperfusion associated with clusters of CSDs was significantly longer than the hypoperfusion occasionally observed with isolated CSDs. The clusters of CSDs also resulted in a profound drop in tissue oxygenation and electrocorticographic activity that did not normalize between the CSDs within the cluster. As demonstrated in an earlier study,[50] the clusters of CSDs were temporally linked to the development of delayed infarcts in the recording areas. These dramatic findings suggest that energy depletion as a result of CSDs may contribute to the pathogenesis of DCI.

CAUSES OF DCI

The evidence suggests that CSD is emerging as a new etiologic factor in the development of DCI after SAH. Additionally, the available data highlight the fact that DCI has a complex pathophysiology in which multiple factors may act in concert to produce brain damage (Figure). Although not the sole cause of DCI, vasospasm may play a role by reducing CBF and lowering the threshold for CSD. Additional factors such as microcirculatory dysfunction, microemboli, and irritating byproducts of hemolysis may provide the final trigger for CSDs. Hypoperfusion secondary to clusters of CSD may lead to a greater mismatch between neuronal energy requirements and energy substrate delivery, enhancing the pathologic cycle and ultimately leading to cerebral infarction (Figure). To realize whether suppressing CSD is a viable therapeutic strategy to prevent DCI requires a more comprehensive understanding of CSD in SAH. If CSD is an early manifestation of neuronal dysfunction after SAH, then treatments that suppress CSD may lead to decreased DCI and improved clinical outcomes. However, if CSD is only manifested after terminal metabolic failure has set in, then therapeutics that target CSD will not revive brain tissue already fated to die.[8]

Nimodipine has been shown in animal studies to correct the inverse hemodynamic response of CSD under pathologic conditions.[45] However, at the doses and formulation used currently in patients with SAH, it is does not prevent all CSDs.[10,50] Some potential targets for the suppression of CSD include *N*-methyl-D-aspartic acid antagonists, correction of cerebral glucose, and hyperoxia. *N*-methyl-D-aspartic acid antagonists alter CSDs and reduce the hypoperfusion associated with the inverse hemodynamic response.[41] However, *N*-methyl-D-aspartic acid antagonists may not be as effective in damaged tissue.[10,39] Reduced glucose levels trigger CSDs experimentally, and correction of glucose levels attenuates CSDs.[43] On the other hand, the relationship between blood glucose and cerebral glucose levels is not straightforward,[51] and hyperglycemia is associated with worse outcomes after SAH.[52] Lastly, hyperoxia has been shown to reduce peri-infarct depolarizations and improve CBF in a mouse model of focal ischemia.[53] Therefore, delivery of increased oxygen may suppress

CSDs after SAH and improve outcome. Oxygen therapy has been studied in acute ischemic stroke but the clinical experience has been mixed,[54] and its efficacy in reducing CSD and improving outcome is still unknown.

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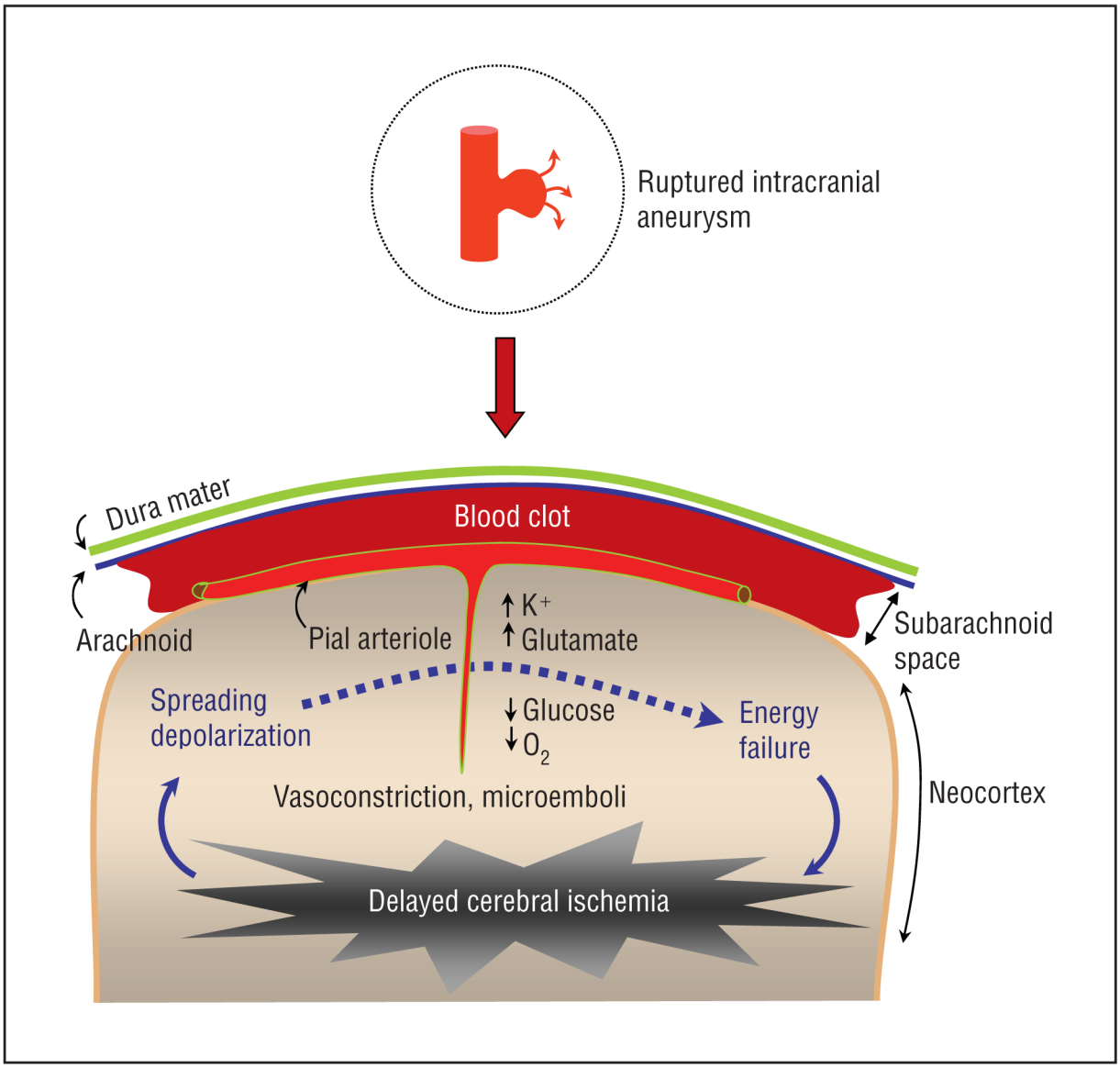

Figure.

Subarachnoid hemorrhage (SAH) is caused by the rupture of saccular aneurysms that develop at the bifurcation of large arteries at the base of the brain. Delayed cerebral ischemia may result from a complex chain of events triggered by the subarachnoid blood. Subarachnoid hemorrhage is associated with a diffuse reduction in cerebral blood flow and brain glucose, possibly due to vasospasm and microvascular dysfunction. Microemboli resulting from increased intravascular clotting may trigger recurring waves of cortical spreading depression. Cortical spreading depressions occurring in the brain damaged by SAH are associated with paradoxical vasoconstriction and tissue hypoxia, as demonstrated by Dreier et al.[10] These ischemic-hypoxic cortical spreading depressions could precipitate brain damage by imposing additional metabolic stress on the energy-depleted brain and by worsening the oxygen and glucose deficits associated with SAH. K^+ indicates potassium ions; O_2, oxygen.