Subarachnoid Hemorrhage
Is It Time for a New Direction?
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Background and Purpose—Despite recent advances in the treatment of patients after subarachnoid hemorrhage, morbidity and mortality rates have failed to improve significantly. Although this was often blamed on vasospasm, is it time to consider alternative etiologies?

Summary of Review—Early brain injury (EBI) is a recently described term that describes the immediate injury to the brain after subarachnoid hemorrhage. A number of pathways have been recognized as having a role in the etiology of EBI. This review provides a brief synopsis of EBI and its implications for the future.

Conclusions—EBI may be responsible for the detrimental effects seen in patients after subarachnoid hemorrhage. Additional studies are needed to determine the pathophysiology of EBI and to explore potential therapeutic options. (Stroke. 2009;40[suppl 1]:S86-S87.)

Key Words: apoptosis • subarachnoid hemorrhage • vasospasm • early brain injury

Subarachnoid hemorrhage (SAH) has been managed by surgical clipping for patients with aneurysmal SAH after it was successfully performed by Dandy in 1937.¹ More recently, aneurysms are now treated with endovascular coiling in the majority of cases. This of course avoids the need for a craniotomy, which has been shown to improve outcome in the short term. Surgical intervention, however, treats the aneurysm but not the SAH itself. There are in fact limited treatment options available for patients with SAH. Each year, ≈10 in 100,000 people experience an aneurysmal SAH. SAH, therefore, is a devastating disease, carrying with it a mortality of 12% before receiving medical attention. With an additional 40% dying within a month of admission to hospital and a 30% morbidity in the survivors, it seems clear that a new approach with regard to the treatment of SAH is warranted.² There are 2 main issues that need to be addressed: these are vasospasm and early brain injury (EBI).

Vasospasm
Vasospasm has been the focus of the majority of research efforts during the past number of decades and there are a copious number of articles on the topic, but unfortunately, this has led to limited success with regard to improving outcome.³ Calcium channel blockers are now the mainstay of prophylaxis for vasospasm. The efficacy of this drug class is certainly debatable, and the true impact it has had on outcome after SAH is also controversial. The Cochrane Group found that for oral nimodipine, the relative risk was 0.67 (95% CI=0.55 to 0.81). However, they concluded that “the evidence for nimodipine is not beyond all doubt, but given the potential benefits and modest risks of this treatment, oral nimodipine is currently indicated in patients with aneurysmal SAH.”⁴ In 2005, a double-blind, randomized clinical trial with clazosentan showed a significant dose-dependent 65% reduction in the relative risk of angiographic vasospasm.⁵ Surprisingly, however, the CONSCIOUS-1 trial failed to demonstrate an improvement in outcome. This has led to questions with regard to the clinical significance of angiographic vasospasm. So much so that some authors have called for a Kuhnian revolution in the field.⁶

Early Brain Injury
EBI is a recent concept that looks at overall brain injury after SAH. There have been a number of recent articles indicating that the pathophysiologic consequences of an aneurysmal SAH lead not only to vasospasm but also to a global ischemic injury to the brain. This is a significant move away from the previous theories of vasospasm as being the main consequence of SAH, leading to neurologic deficits. Furthermore, it should be pointed out that EBI may be the primary cause of mortality in SAH patients.⁷ Therefore, it seems that EBI should be considered a primary target for future research. EBI occurs as a result of the impact of an aneurysmal SAH on the brain. A number of key factors occur, including elevation of intracranial pressure, reduction of cerebral blood flow, suppression of cerebral perfusion pressure, fall in brain oxygenation, blood-brain barrier breakdown, brain edema, and neuronal cell death. For an in-depth review of the pathogenesis of...
EIB in relation to SAH, see Cahill et al. The mechanisms behind many of these key events are poorly understood, and there are currently no treatment options available by which they can be prevented or treated. Although these factors have long been understood, their effects and consequences are not. Indeed, many of these factors are presumed to occur in the clinical setting but in fact have only ever been demonstrated in animal models.

There are currently a number of pathways that have been implicated in EBI. These include the apoptotic pathways, inflammatory pathways, and ischemic pathways, to name but a few (see the Figure). In addition, all of these pathways have 1 common outcome, which is cell death. This leads to cortical ischemia, inflammation, neuronal cell death, brain edema, and possibly even vasospasm. What the key factors in this complex relationship are remain to be seen. However, one thing is clear: EBI research is advancing and will continue to do so exponentially as more discoveries are made. Given the fact that the reversal of vasospasm does not appear to improve outcome, it could be argued that the treatment of EBI may have more success. It may be that in the future, anti-EBI treatments will finally provide a viable treatment option for patients with SAH.

**Conclusions**

EBI is likely to be the result of a number of critical pathways that are probably interrelated with a similar end result, cell death. This leads to cortical ischemia, inflammation, neuronal cell death, brain edema, and possibly even vasospasm. What the key factors in this complex relationship are remain to be seen. However, one thing is clear: EBI research is advancing and will continue to do so exponentially as more discoveries are made. Given the fact that the reversal of vasospasm does not appear to improve outcome, it could be argued that the treatment of EBI may have more success. It may be that in the future, anti-EBI treatments will finally provide a viable treatment option for patients with SAH.

**Sources of Funding**

This study was partially supported by grants NS53407 and NS45694 from the National Institutes of Health to J.H.Z. Also, J.H.Z. is a recipient of Bayu Scholar of Chongqing city.

**Disclosures**

None.

**References**

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Stroke. 2009;40:S86-S87; originally published online December 8, 2008;
doi: 10.1161/STR0KEAHA.108.533315
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/3_suppl_1/S86

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