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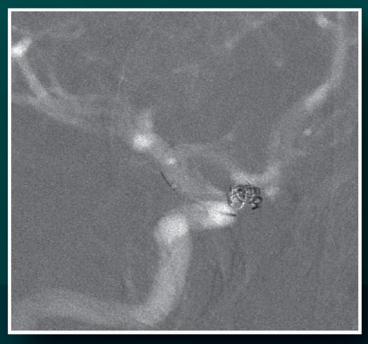
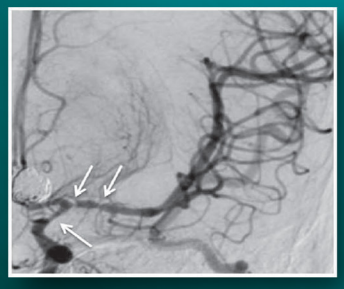
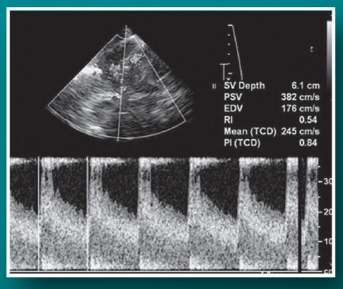
Emily J Gilmore

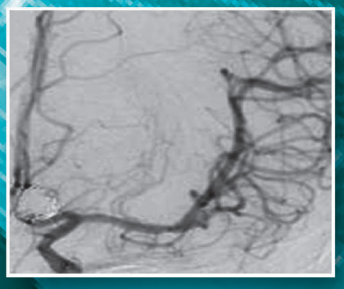




Contemporary Understanding and Management of Cerebral Vasospasm

(A Practical Guide)

Foreword
Dennis D Spencer

CONTENTS

1. **The History of Cerebral Vasospasm** 1
Milo A Hollingworth, Ketan R Bulsara

2. **Definitions and Epidemiology of Vasospasm** 4
Hardik Amin, David M Greer

3. **Recent Topics and Advances in the Molecular Mechanisms Contributing to Cerebral Vasospasm in Subarachnoid Hemorrhage** 8
Robert J Claycomb, Kevin N Sheth

Endothelin-1 8; Neuroinflammation and Host Defense 9; Antioxidants and Scavengers of Free Radicals 10; Tenascin-C and Platelet-Derived Growth Factor 10; Inhibition of HMG-CoA Reductase 10; Vasodilators 11; Antiepileptic Drugs 11

4. **The Pathophysiology and Pathology of Cerebral Vasospasm Following Subarachnoid Hemorrhage** 16
David Y Hwang, Anita J Huttner

Anatomic Considerations 16; Morphological Alterations in Cerebral Arteries after Subarachnoid Hemorrhage 17; Pathophysiology of Vasospasm 17

5. **Imaging of Vasospasm: The Role of Magnetic Resonance Imaging in Subarachnoid Hemorrhage-Related Vasospasm** 23
Amit Mahajan, Michele H Johnson

Pathophysiology 23; Techniques and Sequences 24; Magnetic Resonance Perfusion Imaging 24; Limitations of Magnetic Resonance Imaging 26; Hyperacute Magnetic Resonance Imaging Protocol 27; Role of Magnetic Resonance Imaging in Patients with Subarachnoid Hemorrhage 27; Perfusion Imaging 30; Vessel Wall Imaging 30

6. **Imaging of Vasospasm: CT, CTA and CTP Correlated with Digital Subtracted Angiography in Cerebral Vasospasm** 32
Ajay Malhotra, Michele H Johnson

Use of CT, Contrast CT and CTA as Noninvasive Techniques along with TCD and DSA to Identify Probability, Extent and Severity of Vasospasm 33; Technical Features and Scan Acquisition 34; Image Interpretation of Computed Tomography Angiography in Vasospasm 35; Accuracy of Computed Tomography Angiography for Identification and Stratification of Cerebral Vasospasm 38; Computed Tomography Perfusion in Cerebral Vasospasm 38; Limitations, Pitfalls and Problems 40

7. **Imaging of Vasospasm: Transcranial Doppler Ultrasound Imaging: Detecting Intracerebral Arterial Vasospasm** 43
Jonathan D Kirsch, Michele H Johnson, Leslie M Scoutt

Subarachnoid Hemorrhage and Vasospasm Detection 43; Technique 44; Doppler Ultrasound Physics 45; Biosafety 47; Doppler Evaluation of Vasospasm 48; Other Applications of Transcranial Doppler Imaging 52

8. Medical Management of Vasospasm 55
Evie Marcolini, Emily J Gilmore

Defining the Problem 55; Monitoring and Triggers 55; Triggers for Intervention 56; Hemodynamic Augmentation 57; Calcium Channel Blockers 58; Magnesium 58; Endothelin Receptor Antagonists 58; Statins 58; Nitric Oxide 58; Fever Control 59; Hyponatremia 59; Adrenal Insufficiency 59

9. Electroencephalogram Monitoring of Vasospasm 62
Nicolas Gaspard, Emily J Gilmore, Lawrence J Hirsch

Cellular Basis of Electroencephalogram Activity 62; Modifications of Brain Metabolism and Electroencephalogram Activity Secondary to Ischemia 62; Electroencephalogram Studies in Patients with Aneurysmal Subarachnoid Hemorrhage 63; Continuous Electroencephalogram Monitoring for Ischemia Detection 63; Quantitative Electroencephalogram Analysis with the Fast Fourier Transform 64; Artifacts and the use of Intracortical Electroencephalogram 67; Other Confounding Factors and the Need for Multimodality Monitoring 67; Continuous Electroencephalogram for the Monitoring of Treatment 68; Future Developments 68

10. Anesthesia for Neurointerventional Surgery 70
Keith J Ruskin

Anesthetic Management 70; Radiation Protection 73

11. Practical Microsurgical and Endovascular Treatment of Vasospasm 75
Ryan A Grant, Ketan R Bulsara, Charles C Matouk

Pathogenesis of Cerebral Vasospasm 75; Medical Prevention and Treatment of Cerebral Vasospasm 76

12. Special Populations 85
Lauren A Beslow, Jonathan D Kirsch

A. Pediatric Subarachnoid Hemorrhage 85
Lauren A Beslow

B. Sickle Cell Disease 86
Jonathan D Kirsch

***Appendix:* Clinical Protocols** 89

Subarachnoid Hemorrhage Protocol 89
Vasospasm Protocol 91
Abbreviations 92

Index 95

Chapter 3

Recent Topics and Advances in the Molecular Mechanisms Contributing to Cerebral Vasospasm in Subarachnoid Hemorrhage

Robert J Claycomb, Kevin N Sheth

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a relatively common neurological condition that occurs in nearly 300,000 people each year in the United States.[1,2] Approximately 40% of aSAH patients die. Cerebral vasospasm occurs in approximately 70% of all SAH cases and contributes significantly to the morbidity and mortality of aSAH patients.[3] Despite intensive research, the full pathophysiology contributing to SAH-associated vasospasm remains. This chapter will primarily focus on the recent and novel experimental treatments of SAH-induced vasospasm and new concepts describing the underlying molecular mechanisms contributing to SAH-induced cerebral vasospasm with particular attention to those studies published within the past 5 years.

ENDOTHELIN-1

One of the most studied molecules in the pathogenesis of cerebral vasospasm is the potent vasoconstrictor endothelin-1 (ET-1).[4-10] ET-1 is a soluble, 21-amino acid peptide that was initially described as a vasoconstrictor isolated from vascular endothelial cells[10] and has since been described to be expressed in the endothelial cells of essentially all vascular beds including those of the cerebral vasculature.[11,12] Multiple proteolytic steps are necessary for the maturation of ET-1, the last of which is catalyzed by endothelin-converting enzymes (ECEs).[13] ET-1 is thought to exert its vasoconstrictive properties by interaction with endothelin receptor A (ETA),[14] which is predominantly expressed on vascular smooth muscle cells.[15,16] A second endothelin receptor B (ETB) is primarily expressed on endothelial cells and is thought to participate in vasodilation.[16] The interaction of ET-1 with its receptor results in the activation of multiple signal transduction pathways including protein kinase C (PKC), Ras and extracellular signal-regulated kinase 1 or 2 (ERK1/2) and adenylate cyclase.[4]

Given its ability to promote rapid vasoconstriction within the cerebral vasculature, the role of ET-1 in SAH-induced vasospasm has been extensively researched. Specifically, in both experimental animal models of aSAH and aSAH patients, levels of ET-1 have been described to be increased within the cerebrospinal fluid (CSF) and sera.[17-22] However, from these studies the causal relationship between ET-1 expression and cerebral vasospasm is unclear. It is possible that the increased ET-1 levels result from the damage caused by cerebral vasospasm as opposed to ET-1 being the culprit in the vasospasm cascade.[4,23] Indeed, ischemic stroke alone has been described to cause elevations in ET-1[24] and in a primate model of aSAH, it was suggested that levels of ET-1 within the CSF did not increase prior to vasospasm but did increase after cerebral ischemia.[25]

Despite some evidence against the causal contribution of ET-1 to aSAH-associated cerebral vasospasm, inhibition of the ET-1 pathway has been a target in the pathogenesis of vasospasm. Several preclinical studies demonstrated that inhibitors of ECEs (phosphoramidon, CGS 26303, CGS 26393 and CGS 35066), which presumably act by decreasing the production of mature ET-1, do in fact reduce aSAH-induced vasospasm in canine and rabbit models.[26-31] To date there have been no human clinical trials with these drugs; however, they are still considered viable targets for potential future treatment trials of cerebral vasospasm.[4,32]

More recently, clinical trials of ET-1 receptor antagonists have been performed. The first of which used the nonspecific receptor antagonist bosentan, which inhibits both ETA and ETB. In a trial of 24 patients with aSAH, more patients treated with bosentan had a reduction in mean cerebral flow velocities as compared to those treated with placebo, suggesting that less vasospasm was occurring in the treated patients.[33] Additionally, high-dose bosentan for the treatment of aSAH-associated vasospasm was determined to be safe and caused no significant hypotension in a recent study of 10 aSAH patients; however, four of those patients treated with bosentan did develop clinically significant cerebral vasospasm.[34] No further clinical studies have been performed using bosentan presumably due to the availability of a selective ETA antagonist, clazosentan.

Clazosentan is a selective ETA antagonist that has been extensively studied in a series of clinical trials called

CONSCIOUS (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring after Subarachnoid Hemorrhage).[35,36] It was proposed that selective inhibition of ETA by clazosentan would reduce vasospasm because the ETA subtype of ET-1 receptor primarily participates in vasoconstriction whereas ETB typically induces vasodilation.[35-37] The initial phase 2 randomized, double-blind, placebo-controlled trial (CONSCIOUS-1) offered promising results. Clazosentan decreased the incidence of severe vasospasm, the occurrence of delayed ischemic neurologic deficits, and the incidence of new infarcts seen on computed tomography (CT) scans in a dose-dependent fashion. More specifically, the incidence of moderate or severe vasospasm in SAH patients was reduced from 66% in the placebo group to 23% in the high-dose clazosentan group.[35] This correlated to a relative risk reduction of 65% in the highest dosed group.[35] Moreover, while not statistically significant, nor powered for such an endpoint, there was a clear trend toward a reduction in mortality in the clazosentan-treated cohort compared to the placebo-treated aSAH patients.[35] Following CONSCIOUS-1, there were two phase III trials, CONSCIOUS-2 and CONSCIOUS-3. Unfortunately, CONSCIOUS-2 did not replicate the findings of its predecessor.[36] In fact, in this larger (1,157 aSAH patients) randomized, double-blinded placebo-controlled study, clazosentan had no significant effect on mortality or cerebral vasospasm-related morbidity 6 weeks after aSAH (primary endpoint). Though clazosentan was linked to a 17% relative risk reduction in the primary endpoint, this did not translate into improved functional outcome at the 12 weeks as reflected by the Glasgow Outcomes Score Extended (secondary outcome). Other pathological processes that contribute to the development of delayed neurological deterioration were implicated in the negative outcome of the study.[36] This negative finding resulted in the CONSCIOUS-3 trial, which had hoped to look at different doses of clazosentan, being stopped prematurely after only 577 of the anticipated 1,500 patients were enrolled. The results of CONSCIOUS-3 were recently published and were similar to CONSCIOUS-2.[4]

Despite the inability of the ET-1 antagonist clazosentan to improve functional outcome of SAH patients in the CONSCIOUS trials, other methods to manipulate the ET-1 axis are still under investigation. Sun et al. have suggested that PKC activation occurs during aSAH-induced cerebral vasospasm and leads to the surface expression of the ET-1 receptors, ETA and ETB.[38] Furthermore, administration of a selective PKC inhibitor (RO-31-7549) to rats after experimentally induced aSAH not only decreased the expression of ETA and ETB, but lead to an increase in the caliber of the basilar artery, suggesting that reduction in ET-1 receptor expression by inhibition of PKC may lead to mitigation of vasospasm.[38]

NEUROINFLAMMATION AND HOST DEFENSE

Aneurysmal SAH is typically associated with a robust inflammatory response within the subarachnoid space. Once red blood cells enter this space, they rupture and release highly toxic, free hemoglobin (Hb) which initiates host defense mechanisms and inflammation.[39-41] It is hypothesized that the inflammation in the subarachnoid space causes damage to the neighboring endothelium of cerebral blood vessels resulting in the release of ET-1[21,40] and depletion of the endogenous vasodilator nitric oxide (NO),[42,43] which contributes to cerebral vasospasm.[40,41] The precise molecular pathways involved in the inflammation associated with aSAH are still under intense investigation; however, there are several emerging targets that may lead to new therapies.

First, a recent study investigated the effect of blockade of interleukin-1β (IL-1β), the predominant proinflammatory cytokine of the central nervous system (CNS),[44] on aSAH-associated vasospasm. IL-1β blockade resulted in a reduction in the degree of basilar artery vasospasm caused by experimentally induced aSAH in rats.[45] This study suggests that reduction of IL-1β activity may be a viable target for intervention, especially considering that a selective IL-1β antagonist (anakinra) is already used to treat other inflammatory diseases.[44]

Another signaling pathway that has been implicated in aSAH-associated vasospasm is mammalian target of rapamycin (mTOR). Briefly, mTOR signaling is hypothesized to participate in cellular proliferation, growth and survival.[46,47] In the setting of endothelial cell damage, as would occur during aSAH, levels of mTOR increase which promotes the proliferation of new vascular cell walls that could theoretically then participate in vasospasm.[46,47] Therefore, Zhang et al. proposed that aSAH-associated vasospasm may be reduced if the production of new vascular walls was inhibited via reduction in mTOR signaling.[47] Indeed, not only did inhibition of the mTOR pathway lead to a reduction in the degree of vasospasm in a canine model of aSAH, but the experimental animals had improved neurological outcomes as compared to control-treated animals.[47]

Another emerging target is the sulfonylurea receptor 1 (Sur1).[48] Sur1 is a unique adenosine triphosphate (ATP)-binding cassette (ABC) protein that can regulate various voltage-gated ion channels and this regulation can be inhibited by sulfonylurea drugs such as glyburide.[48] It is thought that Sur1 may contribute to neuronal injury via its association with NCCa-ATP (nonselective cation channel that is regulated by intracellular calcium and ATP).[48,49] The Sur1-NCCa-ATP channel has been associated with prolonged neuronal membrane depolarization and oncotic cell death in multiple in vitro models.[48-50] Relevant to this discussion, levels of Sur1 have been described to be increased within the vasculature and neurons of rats in an experimental model of aSAH.[51] Moreover, inhibition of Sur1 by glyburide resulted in a reduced production of inflammatory cytokines, decreased activation of inflammatory pathways and blunting of the aSAH-associated inflammation evidenced by normalized vasculature permeability and extravasation of serum proteins.[51] Overall, this study suggests that aSAH-associated inflammation can be reduced by inhibition of Sur1 by glyburide, a commonly used antihyperglycemic medication. Although it has not been specifically linked to aSAH-associated vasospasm to date, it remains an attractive therapeutic target.

In addition to reducing the specific inflammation associated with subarachnoid blood in aSAH, reduction of systemic inflammation also may benefit aSAH patients.[52] Further analysis of the CONSCIOUS-1 trial demonstrated that the development of systemic inflammatory response syndrome (SIRS) conferred a worse outcome and it was not necessarily associated with an increased risk of vasospasm further adding to the literature that factors other than vasospasm clearly contribute to delayed neurological deterioration in aSAH patients.[52]

ANTIOXIDANTS AND SCAVENGERS OF FREE RADICALS

As previously mentioned, once red blood cells enter the subarachnoid space their lysis causes a vast amount of free Hb to be released. Due to its iron content, this produces hydrogen peroxide, hydroxyl radicals and superoxide anions via Fenton and Haber-Weiss reactions.[39,53] Not only do these cause direct damage but they are thought to activate pathways that can directly contribute to aSAH-associated vasospasm.[53,54] Because of this, several novel therapeutic approaches have been trialed specifically to decrease the amount of free radicals and reactive oxygen species ultimately to decrease inflammation and to reduce vasospasm in aSAH.

First, one of the most commonly used clinical antioxidants, N-acetylcysteine (NAC), was recently trialed in a rabbit model aSAH.[55] NAC is thought to work by contributing to the regeneration of glutathione, a powerful endogenous antioxidant, which then can act to reduce the levels of damaging free radical and other oxidative species.[55] Not only did NAC reduce lipid peroxidation, a measure of oxidative damage, but it led to a decrease in histological evidence of vasospasm,[55] suggesting that the production of reactive oxygen species may contribute to aSAH-associated vasospasm.

Another such study performed by Hong et al. determined the effect of hydrogen-rich saline in a model of experimental aSAH in rats.[56] It was proposed that the hydrogen contained in the saline would serve as a potent antioxidant, thereby decreasing cerebral vasospasm and inflammation.[56] Indeed, the rats treated with hydrogen-rich saline demonstrated less histologically determined basilar artery vasospasm, decreased lipid peroxidation and expression of proinflammatory cytokines and had improved neurological outcomes as compared to control rats.[56] Again, this study highlights the contribution of reactive oxygen species to cerebral vasospasm.

Finally, curcumin is a widely used medicinal spice that has been previously described to attenuate CNS inflammation in diverse disease processes such as ischemic stroke and traumatic brain injury.[57,58] Recently, curcumin has been described to attenuate aSAH-associated vasospasm and inflammation in an experimental mouse model of aSAH[59] and to decrease mortality and neurotoxicity in an experimental rat model of SAH.[60] Interestingly, in the study conducted by Wakade et al., a significant reduction in the degree of vasospasm did not improve the neurological outcomes of the experimental animals.[59]

The underlying mechanism of vasospasm due to reactive oxygen species is still unclear; however, one recent report has implicated the signal transducer and activator of transcription 1 (STAT1).[61] Osuka et al. demonstrated that STAT1 is rapidly upregulated in the basilar arteries in an experimental rat model of aSAH. Furthermore, this increased expression was blocked by administration of edaravone, a potent antioxidant that has been previously described to attenuate aSAH-associated vasospasm.[61,62] Although this study did not specifically examine vasospasm associated with experimental aSAH, it does suggest that STAT1 may contribute to vasospasm given its previously described roles in arterial remodeling.[63]

TENASCIN-C AND PLATELET-DERIVED GROWTH FACTOR

Another novel molecule that may contribute to aSAH-induced vasoconstriction is tenascin-C (TN-C). Briefly, TN-C is an extracellular matrix protein that is thought to contribute to neuroinflammation by interacting with immune cells and previous research has implicated its actions in diverse CNS processes such as multiple sclerosis, traumatic injury and synaptic plasticity.[64] More recently, it has been implicated in vasoconstriction associated with aSAH. The level of TN-C protein was found to be increased within spastic arterial walls in a rat model of aSAH[65] and exogenously administered TN-C led to arterial vasospasm in rats,[66] suggesting that this molecule may play a direct role in vasospasm. Furthermore, in humans with aSAH, the levels of TN-C were found to be increased within the serum and CSF implying that induction of TN-C protein during SAH is not restricted only to experimental animal models.[65,67] Finally, pharmacologic reduction of TN-C after experimentally induced aSAH in rats was associated with a reduction in the degree of vasospasm and improved neurological outcomes in the experimental animals.[68] Interestingly, because there are no known direct inhibitors of TN-C, the aforementioned study achieved TN-C reduction indirectly using imatinib, a nonspecific tyrosine kinase inhibitor.[69] Imatinib was used to inhibit platelet-derived growth factor (PDGF), which is a potent inducer of TN-C,[70] thereby indirectly decreasing TN-C expression.[68]

Intriguingly, prior to this association with TN-C, PDGF has been implicated independently in aSAH-associated vasospasm. PDGF has been described in aSAH modeled basilar artery vasospasm in rats where inhibition of endogenous PDGF by a specific inhibitor, trapidil, transiently reduced vasospasm.[71,72] Therefore, inhibition of PDGF activity or reduction of TN-C function directly or indirectly via PDGF inhibition may be viable future targets of therapies geared to suppress aSAH-associated cerebral vasospasm.

INHIBITION OF HMG-CoA REDUCTASE

Introduced clinically in the 1990s, medications that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (collectively called statins) were initially used to reduce serum

cholesterol as a way to reduce adverse cardiovascular events.[73,74] Since then, these medications have been implicated in the possible treatment of several other cardiovascular, metabolic and neurological diseases,[75-78] including aSAH-induced cerebral artery vasospasm. In a small, randomized placebo-controlled trial of 19 patients with aSAH, simvastatin was associated with lower peak mean middle cerebral artery velocities and simvastatin-treated patients had a lower incidence of clinically significant cerebral vasospasm.[79] Moreover, pravastatin was also found to be associated with a decrease in the incidence of vasospasm and mortality, and pravastatin use was found to be associated with improved neurological outcomes in a double-blinded placebo-controlled study of 40 pravastatin-treated patients.[80] More recently, three additional placebo-controlled double-blinded clinical studies failed to show statistically significant reductions in aSAH-associated cerebral vasospasm, mortality or improved neurological outcomes.[81-83] However, this may be due to the low numbers of patients enrolled in each of those studies. Although statistical significance was not achieved, each study demonstrated a trend that suggested patients who received statin therapy benefited. The neurocritical care community anxiously awaits the results of the Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH), a multicenter randomized controlled clinical phase III trial and High-Dose Simvastatin in Aneurysmal Subarachnoid Hemorrhage (HDS-SAH) for more definitive results regarding the neuroprotective and neurovascular benefits of statin medications in the treatment of aSAH-associated vasospasm.

The overall mechanism of statins to reduce aSAH-associated vasospasm is poorly understood. The most recent studies suggest that in addition to their broad anti-inflammatory properties, statins may also increase the availability of NO, a powerful vasodilator, by increasing the expression of endothelial NO synthase (eNOS);[84,85] however, this remains an area of active research.

VASODILATORS

Voltage-gated calcium channel antagonists such as nimodipine and nicardipine have been extensively used in the past for treatment of aSAH-induced cerebral vasospasm; however, their prevention of vasospasm has been incompletely effective.[86,87] Recent studies have trialed dantrolene (an intracellular calcium channel antagonist) or have employed different routes of nimodipine administration. First, Muehlschlegel et al. conducted a small prospective, open-label study in which intravenous dantrolene was administered to aSAH patients.[88] Dantrolene is a ryanodine receptor antagonist; ryanodine receptors are located in the endoplasmic reticulum membrane and release calcium intracellularly. This release of calcium then contributes to smooth muscle contraction. It was proposed that dantrolene would more effectively inhibit vasospasm by blocking intracellular calcium efflux, thereby reducing smooth muscle contraction within the cerebral vasculature.[88] In fact, aSAH patients who received dantrolene did experience some reduction in vasoconstriction.[88] Interestingly, another study has recently demonstrated that certain genetic polymorphisms of the ryanodine receptor (6178G > T) confer an increased risk of cerebral vasospasm in the setting of aSAH.[89] Perhaps this increased risk found in aSAH patients with the 6178G > T polymorphism is associated with an increased efflux of calcium into the intracellular space and this subset of patients may benefit from therapy directed more specifically at antagonism of the ryanodine receptor such as dantrolene.

Nitric oxide is an intrinsic potent vasodilator that is critical to maintaining normal hemodynamics. Through a complex signaling cascade, NO relaxes smooth muscle fibers and dilates cerebral arterioles. It is synthesized by three different enzymes in the body and is upregulated following aneurysmal rupture. Prior studies have suggested that cisternal blood sequesters NO given his tight binding capacity. When bound to Hb, NO is incapable of functioning in its role of regulating normal vascular tone, thus resulting in vasoconstriction.[42] Experimental evidence indicates that NO is protective against angiographic vasospasm and clinical evidence suggests that NO donors like nitroglycerin improve neurologic outcomes after aSAH. Thus, NO remains a potential target for the development of future therapies.

Alternative delivery systems of nimodipine have also been recently trialed. Specifically, Onal et al. demonstrated that intra-arterial and intrathecal administration of nimodipine were more effective than oral or intravenous nimodipine in reducing basilar artery vasospasm in an experimental rabbit model of aSAH.[90] Additionally, the efficacy of nimodipine eluted from prolonged-release microparticles was tested in an experimental model of aSAH.[91] It was demonstrated that nimodipine can be effectively delivered with microparticles and this treatment was associated with a reduction of vasospasm compared to untreated controls.[91] Importantly, histological analysis showed that the microparticles themselves did not cause any tissue injury.[91] Unfortunately, a direct comparison between prolonged-release nimodipine from microparticles and more standard nimodipine administration was not performed.[91]

ANTIEPILEPTIC DRUGS

Two commonly used antiepileptic drugs (AEDs) have recently been suggested as possible novel therapies to reduce the damage caused by aSAH-induced vasospasm. First, lamotrigine (an antiseizure medication that inhibits both voltage-gated calcium and sodium channels) was demonstrated to reduce basilar artery vasospasm and to decrease the amount of hippocampal neuronal degeneration in a rabbit model of aSAH, suggesting that this common drug could benefit patients with aSAH.[92] Another AED, topiramate, was also studied using the same rabbit model of aSAH and although rabbits treated with topiramate had significantly less severe hippocampal injury, there was no evidence of reduction of basilar artery vasospasm.[93] It is hypothesized that the apparent neuroprotective effects of topiramate are derived from its ability to prevent neuronal depolarization, which

may participate in neuronal cell death.[93] Despite the inability of topiramate to affect vascular tone in aSAH, it still may be a useful drug due to this apparent neuroprotective effect.

CONCLUSION

Despite advances in our understanding of the molecular mechanisms contributing to aSAH-associated cerebral vasospasm, several key issues remain unresolved. Most interesting is the possible disconnect between treatment of vasospasm itself and patient outcomes. As previously mentioned, in an animal model of aSAH-associated vasospasm, the experimental drug curcumin decreased vasospasm; however, the curcumin-treated rodents did not have improved neurological outcomes.[59] Furthermore, a recent meta-analysis investigated whether it is the efficacy of vasospasm treatment is associated with positive neurological outcomes.[94] The study examined 14 separate trials of aSAH patients treated with specific experimental therapies designed to reduce cerebral vasospasm.[94] The results from the individual trials were combined to determine whether reduction of cerebral vasospasm, regardless of therapy improved clinical outcomes.[94] Surprisingly, despite statistically significant reduction in vasospasm, there was no improvement in the overall clinical outcome of patients.[94] Although this result may be due to the limited number of studies fulfilling the criteria of the meta-analysis or other methodological factors, this finding suggests that reduction of cerebral vasospasm is one of several mechanisms that likely contribute to the overall clinical outcomes of aSAH patient and that it will remain a highly active topic of research going forward.

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Ketan R Bulsara is an Associate Professor, Department of Neurosurgery, Yale-New Haven Hospital, USA. He is a board certified Neurosurgeon. He is one of only a select few neurosurgeons in the world who is dual fellowship trained in skull-base/cerebrovascular microsurgery and endovascular neurosurgery. He has won numerous awards from the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. He has consistently been listed as one of the top Physicians and Surgeons in the United States by the Consumer Research Group of America based in Washington DC. Prior to his appointment at Yale, he directed the Walter Dandy Neurosurgical Intensive Care Unit and served as the Director, Skull-Base and Cerebrovascular Neurosurgery, University of Missouri-Columbia, USA.

He has over 100 peer-reviewed publications, authored three books, and is a frequent invited lecturer both nationally and internationally. His clinical practice focuses on cerebrovascular/skull-base pathologies with his neurosurgical practice combining microsurgical, skull-base, and endovascular techniques. His research interests focus on cerebral vasospasm, microsurgical anatomy, and development of novel endovascular technologies specifically stents.



Emily J Gilmore is a board certified Neurologist with subspecialty training in neurocritical care and electrophysiology. She completed her residency and fellowship training at the Neurological Institute of New York, Columbia Presbyterian Medical Center and joined (2012) as an Assistant Professor, Department of Neurology, Yale-New Haven Hospital, USA. Her research interests center on the use of continuous EEG monitoring in comatose patients with and without acute brain injury not only to detect subclinical seizures, but also to understand the physiologic underpinnings of the neurologic manifestations of systemic illness, in particular, sepsis-associated brain dysfunction.

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