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Abstract

Despite recent advances, cerebral vasospasm and delayed cerebral ischemia (DCI) still represent a major cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH). Although a significant portion of the morbidity and mortality associated with aSAH is related to the initial hemorrhagic ictus, cerebral vasospasm and DCI are still the leading cause of poor outcomes and death in the acute posthemorrhage period, causing long-term disability or death in more than one in five of all patients who have suffered aSAH and initially survived.

Management of patients following aSAH includes four major considerations: (1) prediction of patients at highest risk for development of DCI, (2) prophylactic measures to reduce its occurrence, (3) monitoring to detect early signs of cerebral ischemia, and (4) treatments to correct vasospasm and cerebral ischemia once it occurs. The authors review the pertinent literature related to each, including both the current management guidelines supported by the literature as well as novel management strategies that are currently being investigated.

Keywords

► vasospasm
► subarachnoid hemorrhage
► stroke
► delayed cerebral ischemia

Epidemiology and Impact

Despite recent advances, cerebral vasospasm and delayed cerebral ischemia (DCI) still represent a major cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH). In general, aSAH affects ∼ 30,000 North Americans annually, representing 5 to 10% of all cases of stroke, primarily affecting individuals aged 40 to 60 years although it can occur at all ages.[1,2] Although aSAH is less common than ischemic forms of stroke, it commonly affects younger patients and therefore is often associated with an even greater impact in terms of productive life years lost and higher medical costs in both the acute and follow-up periods.[3,4]

Although a significant portion of the morbidity and mortality associated with aSAH is related to the initial hemorrhagic ictus, cerebral vasospasm and its related cerebral injury, which typically occurs within 3 to 7 days of hemor-

rhage and can last through 21 days posthemorrhage,[5] is still the leading cause of poor outcomes and death in the acute posthemorrhage period, causing long-term disability or death in more than one in five of all patients who have suffered aSAH and initially survived.[6]

Following aSAH, angiographically detectable vasospasm of the cerebral arteries occurs in 50 to 90% of patients.[7] Approximately two-thirds of aSAH patients will suffer from vasospasm that is at least moderate in severity. Although some of these cases will remain asymptomatic, of these, approximately half will become symptomatic and half of these will develop neuroimaging findings of cerebral infarction, correlating strongly with poor outcomes in these individuals.[8] Although recent advances in the acute management of patients following aSAH have reduced the incidence of these poor outcomes related to cerebral vasospasm, it still remains a leading cause of clinical deterioration and poor outcomes following aSAH. Most recent studies demonstrate an overall risk of death and

permanent disability due to vasospasm alone at close to 10% of patients.[9–11]

Looking Beyond Simple Arterial Spasm

Vasospasm and DCI can be categorized angiographically and clinically.[12] Although a large percentage of aSAH patients demonstrate evidence of arterial spasm on angiographic imaging, a significant portion of these patients do not become symptomatic and are therefore not considered to have clinical vasospasm or DCI. Clinical vasospasm is characterized by new neurologic symptoms, such as mental status changes and/or focal neurologic deficits, that occur in a delayed fashion following aSAH and cannot be explained by other causes such as hydrocephalus, seizures, hypoxia, or metabolic abnormalities.[13] The occurrence of clinical vasospasm and DCI follows the same time course as angiographic vasospasm.[14] Because of this close association between vasospasm and delayed neurologic deficits, spasm of the cerebral arteries has traditionally been considered the sole cause of these deficits. However, the presence of vasospasm and its severity do not always correlate well with the presence of ischemia and/or infarction, as some patients with severe angiographic vasospasm remain asymptomatic and others with more-moderate spasm can become symptomatic and develop cerebral infarction.

Recent investigations have cast further doubt on the belief that vasospasm is solely responsible for the delayed neurologic deficits that are common following aSAH. In particular, recent attention has been focused on the multifactorial nature of DCI and neurologic deterioration after aSAH. Although vasospasm alone has been posited as the cause of these problems, treatments focusing only on prevention or correction of vasospasm have not adequately reduced the occurrence of delayed neurologic injury. For example, the clazosentan trial failed to demonstrate a significant improvement in outcomes despite the fact that the endothelin receptor antagonist reduced the rate of angiographically detectable spasm.[15] Conversely, the nimodipine trial did not show a significant change in the risk for angiographic vasospasm,[16] yet a meta-analysis of randomized trials for nimodipine demonstrated that a significant proportion of patients treated with the drug suffered less neurologic deterioration and infarction.[17] Clearly, there are factors other than vasospasm itself at work and we should move away from this wholly "spasmocentric" view of delayed deficits.

Stimulated by these findings that contradict the view that spasm of the arteries alone is responsible for delayed injury, recent literature has aimed to elucidate these other factors that may contribute to this clinical conundrum, including evaluating changes in the brain that occur before DCI becomes clinically significant.[18] In particular, the initial hemorrhagic ictus causes significant changes to the brain and cerebral vasculature that may sensitize brain tissue to subsequent insults that evolve over the following days and weeks after aSAH. Aneurysmal rupture causes a transient increase in intracranial pressure, reducing cerebral blood flow. While these reductions may not be sufficient to cause frank ischemia at that time, it may cause subtle changes that sensitize the brain and increase the likelihood of later injury.[18–20] Additionally, during this period, distal microcirculatory failure may occur as well due to the phenomenon described as "no-reflow."[21] Stagnation of the microcirculation at the capillary level may lead to increased blood viscosity, vessel wall injury, formation of microthrombi, adherence of granulocytes, formation of platelet aggregates, microvascular constriction, oxidative stress and inflammation, excitotoxicity, changes in cellular metabolism, alterations in vascular tone, and increased vascular permeability.[22–34] Consistent with these theories, microvascular constriction has been documented in vessels of 50 to 300 μm in diameter and diffusion-weighted magnetic resonance imaging (MRI) has provided evidence of acute brain injury distal or unrelated to the aneurysm rupture site in patients with poor-grade aSAH.[22,24] Other factors, such as loss of autoregulation, poor native leptomeningeal collaterals, and other patient variations in ischemic tolerance may further contribute to the predisposition to delayed ischemia and neurologic deterioration.[35,36]

Although these new theories of DCI and delayed neurologic injury following aSAH may fundamentally change the way we prevent and/or treat DCI in the future, in current clinical practice attempts to reduce the morbidity and mortality associated with delayed neurologic deterioration requires utilizing adequate techniques to accurately detect risk for and presence of vasospasm as early as possible and initiating treatments that reduce the risk for and occurrence of symptomatic DCI.

Prediction of Vasospasm

Although some studies have attempted to predict which patients are most likely to develop vasospasm following aneurysm rupture,[37,38] no single risk factor or model can accurately predict every case of symptomatic vasospasm. The strongest risk factor for development of vasospasm appears to be the volume of subarachnoid clot present, with patients with larger volume of clot at highest risk.[39,40] Although grading of extent of hemorrhage has traditionally used the Fisher grading scale, a modified scale that attempts to correct some of the problems with the original Fisher Scale has been shown to improve the predictive value for DCI and prognosis in one study.[41]

Several other risk factors have been shown to be predictive of vasospasm. Chief among these is poor neurologic grade on admission, a history of cigarette smoking, and a history of hypertension.[42] Cocaine use has also been found to be an independent predictor of vasospasm; it has also been suggested that individuals of Japanese ethnicity may be at greater risk.[43,44] Other factors, such as gender, age, and aneurysm location have also been investigated, but were found to have an unlikely relationship to vasospasm.

Finally, the treatment modality used for aneurysm protection may impact risk for subsequent vasospasm, with endovascular coiling associated with a slightly lower risk when compared with surgical clipping in one study.[45] However, in that study the difference between the two groups was not robust and no study has yet confirmed this finding.

Vasospasm Monitoring and Diagnosis

To initiate prompt diagnosis and treatment for vasospasm, careful screening of patients following aSAH should be performed to identify its onset during the first few weeks after aneurysm rupture. The ideal protocol for vasospasm detection has yet to be elucidated; however, several investigations can aid in the diagnosis of vasospasm.

Although daily digital subtraction angiography and/or high-definition computed tomography (CT) angiography are the most direct techniques to diagnose spasm of the intracranial arteries and its routine use in all patients may theoretically be a good way to identify all cases of vasospasm as early as possible, the invasive nature, dye exposure, and potential complications associated with these procedures preclude their use as a general screening method. In select patients, particularly those at high risk for vasospasm, those who have become symptomatic, and those for whom balloon angioplasty or endovascular infusions are being considered, properly timed angiography is an important adjunct to routine monitoring. So though cerebral angiography is an important technique to work up those patients with other monitoring evidence of vasospasm, other less-invasive techniques should be utilized routinely for screening purposes.

Physical Examination

The simplest form of vasospasm monitoring involves vigilant bedside examination of patients throughout the period of greatest risk for vasospasm and DCI. Frequent examination should be performed to establish each patient's baseline neurologic status following aSAH and to detect any changes, however subtle. Subtle changes in mental status as well as focal neurologic deficits, including subtle asymmetries in strength as indicated by the presence of a pronator drift, require additional attention. Newly identified deficits should be worked up immediately to rule out other potential causes, such as hydrocephalus, seizures, and metabolic abnormalities.

Although this form of clinical monitoring can catch the gradual onset of DCI in many patients in its early stages, it is far from complete. For one, it fails to identify vasospasm early in most cases, as the initial onset of vasospasm may not be associated with significant outward signs or symptoms. Second, identifying subtle neurologic deficits may be difficult or impossible in patients who are already significantly neurologically impaired due to the initial hemorrhage. Although a subtle change in mental status or muscle strength may be more obvious in a low-grade patient who is conscious and able to participate in the examination, the same changes may not be apparent in a patient who is obtunded or comatose. For these reasons, physical examination cannot be the only monitoring technique utilized to screen for vasospasm.

The recently published and updated American Heart Association and American Stroke Association (AHA/ASA) guidelines for the management of aSAH list only two recommended techniques that the current literature supports for routine monitoring (►Table 1): transcranial Doppler (class IIa; level of evidence B) and perfusion imaging with CT or magnetic

Table 1 AHA/ASA Guidelines for the Management of aSAH: Recommendations for Vasospasm and DCI Monitoring and Diagnosis[46]

1. Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm (class IIa; level of evidence B)
2. Perfusion imaging with computed tomography or magnetic resonance can be useful to identify regions of potential brain ischemia (class IIa; level of evidence B)

Abbreviations: AHA, American Heart Association; ASA, American Stroke Association; aSAH, aneurysmal subarachnoid hemorrhage; DCI, delayed cerebral ischemia.

resonance to identify regions of potential brain ischemia (class IIa; level of evidence B), both discussed below.[46]

Transcranial Doppler

Transcranial Doppler (TCD) offers a noninvasive means to evaluate the status of the intracranial vasculature and has become one of the mainstays of vasospasm monitoring in the intensive care unit at many centers. Transcranial Doppler is recommended as a reasonable option to monitor patients for the development of vasospasm.[46,47] When proximal cerebral arteries narrow, the velocity of blood flow in that artery increases and this is detectable on TCD. Although the absolute velocity of blood flow in the middle cerebral artery (MCA) shows a strong correlation with the lack or presence of vasospasm when it is clearly very low (< 120 cm/s; low risk for vasospasm) or very high (> 200 cm/s; high risk for vasospasm), with a negative and positive predictive value close to 90%, absolute velocity does not correlate as well in the intermediate range. It is also inadequate to identify spasm of more distal arteries and the velocity can be subject to changes due to overall changes in cerebral blood flow (CBF).

Two indices have been developed in an attempt to improve the predictive value of TCD in these cases. The Lindegaard ratio is represented by the MCA velocity compared with the velocity in the proximal internal carotid artery (V_{MCA}/V_{ICA}).[48] A value of greater than 3 is considered consistent with vasospasm. Additionally, the ratio of the TCD velocity to overall CBF (as measured by the ^{133}Xe inhalation bedside technique) has also been used to distinguish hyperemia from true vasospasm.

Although TCD is recommended for routine daily monitoring for vasospasm, confirmation with cerebral angiography should be performed, particularly in intermediate cases for which the predictive value of TCD is lacking.

Cerebral Blood Flow and Perfusion Imaging

Imaging with various methods of perfusion CT, MRI and/or positron emission tomography (PET) are increasingly used to predict or confirm the presence of vasospasm and resulting DCI.[37,49–55] The recent aSAH guidelines recommend their use as a potential adjunct to identify regions of potential brain ischemia.[46] However, the cost and difficulty of obtaining such studies in critically ill patients may preclude their use as a routine screening method and are more likely to be used as

confirmation of cerebral ischemia after vasospasm has been detected by other methods.

Another method of CBF monitoring, thermal diffusion flowmetry, has the advantage of providing continuous monitoring of brain perfusion at the bedside.[56] Although this method may be useful for those patients with poor neurologic grade who cannot be monitored adequately by neurologic examination, it is limited by the fact that the probe only measures regional blood flow in the area it is inserted, typically the frontal lobe. Vasospasm in other vascular territories may therefore be missed by this method.

Microdialysis

Insertion of microdialysis probes in the brain to detect cerebral tissue changes in glutamate, lactate, pyruvate, glucose, and glycerol has been used to detect metabolic changes associated with ischemia in patients following aSAH.[57–59] However, like thermal diffusion flowmetry, microdialysis only supplies information about metabolic and chemical changes in a relatively small area of the brain. This limitation, coupled with the difficulty in its routine use in all patients, makes microdialysis inadequate as a sole monitoring technique for vasospasm and DCI.

Other Methods

Preliminary investigations have suggested that several other bedside monitoring techniques, such as continuous electroencephalography, jugular venous oxygen saturation monitoring, and near infrared spectroscopy, may be useful in predicting or diagnosing vasospasm and cerebral ischemia following aSAH.[60–63] However, the utility of these techniques has not been definitively established.

Prophylactic Measures to Reduce Secondary Damage after aSAH (►Table 2)

Early Aneurysm Protection

Before monitoring and treatment of vasospasm and delayed deficits should even be considered, the immediate concern following aSAH is to prevent rebleeding of the aneurysm. Complete obliteration of the aneurysm, whenever possible, is the goal of treatment, either by endovascular or surgical techniques. The recent AHA/ASA guidelines for management

Table 2 AHA/ASA Guidelines for the Management of aSAH: Recommendations for Vasospasm and DCI Prophylaxis[46]

1. Oral nimodipine should be administered to all patients with aSAH (class I; level of evidence A)
2. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI (class I; level of evidence B)
3. Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended (class III; level of evidence B)

Abbreviations: AHA, American Heart Association; ASA, American Stroke Association; aSAH, aneurysmal subarachnoid hemorrhage; DCI, delayed cerebral ischemia.

of aSAH recommend treatment as soon as possible following rupture (class I, level of evidence B).[46] The decision to use endovascular coiling techniques versus surgical clipping to accomplish aneurysm occlusion is still a topic of some debate and the decision should be made on a case-by-case basis by a multidisciplinary team of specialists based on specific characteristics of each patient and aneurysm. In addition to decreasing the risk of rebleeding, early treatment of the aneurysm frees the treating physicians to use prophylactic and treatment options for vasospasm that may otherwise be contraindicated in the setting of an unsecured aneurysm, such as hypertensive and hypervolemic therapy.

Nimodipine

Nimodipine, a calcium-channel blocker, has been used prophylactically in an attempt to reduce the occurrence of vasospasm and DCI for many years. Although the initial theory supporting its use was that the medication would prevent vasoconstriction of the cerebral arteries, the nimodipine trial failed to show there was a reduction in the risk of angiographically detectable vasospasm.[16] However, a meta-analysis of randomized trials demonstrated that a significant proportion of treated patients suffered less neurologic deterioration and infarction when on nimodipine.[17] Although the underlying mechanism of nimodipine's neuroprotection has yet to be fully elucidated, the support for its use is strong enough that the guidelines for aSAH management recommend its administration to all patients with aSAH.[46]

Prophylactic Hypervolemic Therapy

The use of induced hypervolemia, hypertension, and hemodilution (referred to as "triple-H therapy") has been a mainstay of treatment for vasospasm for some time. Prophylactic initiation of hypervolemia can improve cerebral blood flow and reduce the incidence of vasospasm and associated DCI. Patients following aSAH have a tendency toward volume contraction and frank hypovolemia should be avoided to maintain adequate cerebral perfusion pressure.[64] However, there is little evidence to support the routine induction of hypervolemia in all patients following aSAH.[65–67] For this reason, the aSAH management guidelines recommend maintenance of euvolemia to prevent DCI, but do not recommend prophylactic hypervolemia.[46]

Statins

HMG-CoA reductase inhibitors, or statins, have typically been used to lower cholesterol levels, but have also been found to exert several effects on vasculature, including improved endothelial function, reduced clot formation, altered inflammatory responses, and even increased cerebral blood flow. Several small randomized trials of statins, particularly simvastatin, in the setting of aSAH have suggested that statins are safe and may be beneficial in reducing the frequency of vasospasm and delayed ischemia, although the results have been somewhat variable. Two small studies of statins administered for 14 days following aneurysm rupture reported a reduction in angiographic vasospasm and delayed

ischemia.[68,69] Furthermore, one of the studies demonstrated reduced infarction rates and mortality in the statin-treated group and these improvements in outcome were maintained at 6-month follow-up.[70] Additionally, cohort studies have found reduced rates of vasospasm and infarction in patients who were taking daily statins at the time of aneurysm rupture. On the other hand, one randomized exploratory study of simvastatin failed to show a benefit.[71] Despite these conflicting results, a recent meta-analysis of available studies did show a reduction in delayed ischemic deficits with statin use, although reduction in vasospasm itself was harder to demonstrate.[72] A larger phase III trial (Simvastatin in Aneurysmal Subarachnoid Hemorrhage [STASH]) is currently in progress to help clarify the impact of statins on the care of patients following aSAH.

Endothelin Receptor Antagonists

Endothelins are known to produce potent and prolonged vasoconstriction and have been implicated in the mechanisms of cerebral vasospasm following aneurysm rupture. Clazosentan, an endothelin-1 receptor antagonist, has therefore been proposed as a potential prophylactic treatment to reduce the occurrence of vasospasm. The results of the CONSCIOUS-1 trial demonstrated a dose-dependent reduction in angiographic vasospasm with prophylactic clazosentan administration.[15] Interestingly, despite this significant reduction in spasm, the study could not demonstrate a significant impact on clinical outcomes of patients at 3 months and only a minimal effect in preventing neurologic deterioration. Although a post hoc analysis with a stricter definition of vasospasm-related stroke showed a possible benefit, a follow-up phase III trial was developed to further investigate the drug. However, the CONSCIOUS-2 Trial, which included only patients treated by surgical clipping, also found no significant benefit in the treated group.[73] A third, phase III trial, CONSCIOUS-3, of patients treated by endovascular coiling was stopped early, also failing to demonstrate a clinical benefit.[74]

Magnesium Sulfate

Magnesium has been found to have neuroprotective properties and has been investigated for preventing ischemic injury following aSAH as well as in acute ischemic stroke. Although several small pilot studies and one phase III trial (IMASH) have had conflicting results in terms of clinical benefit,[75–78] a subsequent meta-analysis failed to show a significant impact on outcomes.[79] A larger phase III, randomized trial is currently underway.

Clot Clearance and CSF Washout Techniques

Various techniques to reduce the amount of clot in the subarachnoid space have shown early promise in reducing vasospasm and its effects. Two recent meta-analyses of several randomized trials of intrathecal infusion of thrombolytics, including recombinant tissue plasminogen activator and urokinase, with or without "head shaking," suggest some benefit to these techniques.[80–82] Likewise, the head-shaking technique along with lumboventricular lavage has also been reported to have beneficial effects in one study.[83]

Whether lumbar drainage alone reduces the rate of vasospasm and DCI remains unclear. One case-control study showed promising effects in reducing clinical vasospasm and improving outcomes and further investigations are ongoing.[84] Finally, fenestration of the lamina terminalis at the time of surgical aneurysm clipping is thought by some surgeons to aid in washout of clot and has been preliminarily shown in one nonrandomized prospective controlled study to reduce both vasospasm as well as subsequent hydrocephalus.[85]

Other Prophylactic Treatments

Although papaverine has fallen out of favor as a vasodilator due to potential neurotoxic effects, a study of controlled-release papaverine pellet implantation in the subarachnoid space at the time of surgical aneurysm clipping showed some promise in reducing vasospasm and DCI.[86] This finding led the way to a single-center, nonrandomized study of extended-release nicardipine implants in the subarachnoid space which likewise demonstrated a reduction in vasospasm and subsequent ischemia.[87]

Prophylactic angioplasty, prior to the development of demonstrated vasospasm, has been shown to be ineffective in improving outcomes.[88] Likewise, prophylactic antiplatelet treatment has failed to reduce morbidity associated with aSAH and vasospasm, as demonstrated by a recent meta-analysis of available data.[89]

Treatments to Correct Vasospasm (►Table 3)

Triple-H Therapies

So-called triple-H therapy has been a mainstay of vasospasm treatment for years. Although hypervolemic, hypertensive, and hemodilution therapies have not undergone any controlled trials of their efficacy, anecdotal evidence suggests that patients suffering symptomatic vasospasm benefit from increased fluid volume and elevated arterial pressure. Furthermore, studies have shown that increased blood volume does in fact improve cerebral blood flow in areas suffering hypoperfusion related to vasospasm, perhaps due to autoregulatory dysfunction that occurs following aSAH.[90] Furthermore, a systematic review of the literature confirmed that these treatments do in fact have a positive impact and that hypertensive

Table 3 AHA/ASA Guidelines for the Management of aSAH: Recommendations for Vasospasm and DCI Treatment[46]

1. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it (class I; level of evidence B)
2. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy (class IIa; level of evidence B)

Abbreviations: AHA, American Heart Association; ASA, American Stroke Association; aSAH, aneurysmal subarachnoid hemorrhage; DCI, delayed cerebral ischemia.

therapy has a more potent effect in improving cerebral blood flow than either hypervolemia or hemodilution.[91]

Despite the lack of randomized trials to confirm their efficacy, the AHA/ASA recommends maintenance of euvolemia and induction of hypertension in patients suffering DCI, except in those patients who have elevated blood pressure at baseline or have comorbid cardiac disease that would preclude its use.[46] In those patients with pre-existing cardiac disease and the elderly, the risk of complications with hypervolemic/hypertensive therapy is increased and includes risk of cardiac failure, pulmonary edema, cerebral edema, and elevated intracranial pressure.[92,93]

Although it is generally accepted that the ruptured aneurysm must be protected by endovascular coiling or surgical clipping prior to initiation of triple-H treatments, some patients may harbor other unprotected, unruptured aneurysms as well. One study has reported that hypertensive and hypervolemic therapy did not increase the rupture risk of these unprotected aneurysms and did not appear to have a negative effect on short-term natural history.[94]

Due to lack of supportive studies, the current AHA/ASA recommendations do not specify which specific treatments or pressor medications should be used to induce hypertension. However, one study has suggested that induced hypertension is more effective at improving cerebral oxygenation than aggressive hypervolemia and that the goal should rather be to maintain euvolemia because more-aggressive hypervolemic treatment is both less effective and carries a higher risk for associated complications.[95]

Endovascular Angioplasty

For significant symptomatic vasospasm in the proximal cerebral arteries, percutaneous transluminal balloon angioplasty is an effective means to immediately produce dilation of the involved artery and increase distal blood flow delivery. However, more-distal arteries cannot be reached reliably and endovascular infusions of vasodilators may be the only option in these cases. Balloon dilation in proximal vessels appears safe, but there are no randomized trials available to confirm its clinical efficacy.[96,97] The current guidelines for management of aSAH state that angioplasty is reasonable in symptomatic patients who do not rapidly respond to medical therapies, including induced hypertension.[46]

Endovascular Infusions

In the past, papaverine was frequently used as an intra-arterial vasodilator to treat symptomatic vasospasm. However, it has fallen out of favor due to its potential for neurotoxicity.[98] Instead, several other vasodilator medications have been used for superselective infusion into affected arteries to treat vasospasm, including calcium channel blockers (such as verapamil, nicardipine, and nimodipine), fasudil hydrochloride, milrinone, and most recently, nitric oxide donors. The primary drawback to these treatments is their relatively short-acting effect. Although the use of these agents has been fairly widespread, there are few definitive studies to support their efficacy in improving outcomes following aSAH, although several nonrandomized case series have reported

clinical efficacy in reducing spasm and reversing neurologic deficits.[99–103] Intra-arterial vasodilator infusions appear generally safe, though verapamil infusion has occasionally been associated with new seizures.[104] Like balloon angioplasty, the AHA/ASA guidelines support use of endovascular vasodilator infusion as a reasonable option for symptomatic patients refractory to hypertensive therapy.[46] Of particular importance is careful monitoring of the intracranial pressure during infusion of these vasodilating agents, as sustained elevation $\sim$ 20 mm Hg may preclude their use. Finally, vasodilator infusion does not necessarily produce immediate vessel dilation on angiography, making it difficult to use angiographic images as surrogate markers of clinical effectiveness.

Aortic Balloons

Two different types of aortic balloon devices have been suggested for treatment of symptomatic vasospasm. Intra-aortic balloon counterpulsation has been used as a cardiac augmentation device to improve blood pressure and diastolic flow in patients with cardiogenic shock. These devices have likewise been shown to improve cerebral blood flow in patients with cerebral vasospasm and concomitant cardiac failure in preliminary studies.[105,106]

A newer device, the NeuroFlo catheter, utilizes a dual aortic balloon to partially obstruct the abdominal aorta, producing reduced blood flow to the lower extremity while augmenting flow elsewhere. Although the mechanism of neuroprotection associated with this device is not clear, the SENTIS Trial has demonstrated safety and beneficial effects including reduced mortality and severe disability rates.[107–109]

Cervical Sympathetic Block

Animal models and a limited case series have suggested a beneficial effect to ipsilateral superior cervical ganglion blockade with local anesthetics in terms of improved cerebral perfusion.[110,111] However, no clinical trials have been performed to confirm its efficacy.

Conclusions

Although cerebral vasospasm remains a significant cause of secondary injury following aneurysmal subarachnoid hemorrhage, numerous advancements in its prevention, diagnosis, and treatment appear to have improved outcomes for these patients over time. Although only three treatments, oral nimodipine prophylaxis, maintenance of euvolemia, and induction of hypertension, have class I evidence in the literature to support their routine use, several other promising therapies have shown early promise, many of which are currently undergoing additional evaluation in clinical trials. Clearly, vigilant monitoring and aggressive, appropriate therapy for vasospasm and DCI can help prevent permanent neurologic disability in many patients.

Despite numerous advances, there are still many questions remaining about the underlying mechanisms of vasospasm and DCI and whether answers will translate into improved treatments in the future. In particular, studies such as the nimodipine and clazosentan studies have raised doubts about

the traditional view that delayed ischemia and deficits are solely related to spasm of the cerebral arteries. Future investigations will be critical to elucidate the other mechanisms, some of which may occur at the time of aneurysm rupture, contributing to delayed neurologic deterioration. A full understanding of these mechanisms may yield novel treatments that further improve the outcomes for patients suffering subarachnoid hemorrhage.

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