Subarachnoid Hemorrhage, Vasospasm, and Delayed Cerebral Ischemia

Prevention, effective monitoring, and early detection are the keys to successful management after subarachnoid hemorrhage.

By Klearchos Psychogios, MD, MSc and Georgios Tsivgoulis, MD, PhD, MSc, FESO, FEAN

Epidemiology and Etiology
Subarachnoid hemorrhage (SAH) represents a detrimental cerebrovascular disease with high mortality and morbidity.

Direct bleeding effects are the most common underlying cause of mortality, and death, in most cases, occurs within 2 days of an initial event. During the past decade, mortality from SAH has declined by approximately 1% per year. Prevention of rebleeding by early repair of any ruptured aneurysm and advances in neurocritical care contribute to this improved outcome. In this new era, the secondary consequences of SAH—vasospasm and delayed cerebral infarction (DCI)—represent important causes of disability and death.

Cerebral vasospasm—the narrowing of the cerebral arteries after SAH—is a common complication that occurs in up to 70% of patients and can be seen with radiographic and ultrasound imaging. Cerebral vasospasm may be present in some patients even in the first 24 hours of the precipitating event but more frequently begins 3 to 4 days after an aneurysm rupture, reaching a peak after 7 to 10 days and resolving spontaneously after 21 days.

Vasospasm is triggered by the breakdown of blood products accumulating in the subarachnoid and perivascular spaces. Oxyhemoglobin in particular, is thought to play a key role through multiple actions, including direct vasoconstriction, release of arachidonic metabolites and endothelin from the arterial wall, inhibition of endothelium-dependent vasodilation through nitric oxide scavenging, damage to perivascular nerves, and promotion of free radical reactions.

There are several reported predictors of vasospasm, including the amount of blood on CT scan, the presence of intraventricular hemorrhage, neurologic impairment as assessed by World Federation of Neurosurgical Societies (WFNS) scale (Table 1), hypertension and temperature on admission, age, smoking, and aneurysm location. Of all these factors, location and thickness of the blood clot as graded by the Fisher CT scale (grade 3/4), are consistently reported as the most powerful predictors of vasospasm. There are controversial data regarding whether treatment method for aneurysm occlusion (clipping vs coiling) has an effect on the risk of subsequent cerebral vasospasm.

Vasospasm can result in DCI, which refers to a new focal neurologic deficit or a persistent (>1 hour) decline in the patient’s Glasgow Coma Scale (GCS) score by 2 or more points according to a recent consensus definition. Vasospasm and DCI are 2 distinct processes. Vasospasm is an angiographic phenomenon (Figure 1) that may or may not manifest clinically and is predictive of DCI. Not all patients with vasospasm, however, develop DCI, which is the clinical (or neuroimaging) manifestation of delayed ischemia. Although DCI is highly correlated with vasospasm, there may be other contributors including microcirculatory constriction, microthrombosis, cortical spreading depression, and delayed cellular apoptosis.

Monitoring
Level and Timing of Assessments
Early detection of neurologic deterioration with both clinical and radiologic assessment is the mainstay of vasospasm management. Every patient with SAH should be in a neurocritical care unit, intensive care unit (ICU), or comprehensive stroke unit that has specific protocols for continued clinical
TABLE 1. MOST USED GRADING SCALES FOR SUBARACHNOID HEMORRHAGE

<table>
<thead>
<tr>
<th>WFNS grading scale</th>
<th>Modified Fisher CT grading scale</th>
<th>VASOGRADE scale</th>
</tr>
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<tbody>
<tr>
<td>WFNS</td>
<td>Fisher group</td>
<td>VASOGRADE</td>
</tr>
<tr>
<td>I</td>
<td>1 Focal or diffuse thin (≤ 1 mm) SAH, no IVH</td>
<td>1-2 Green</td>
</tr>
<tr>
<td>II</td>
<td>2 Focal or diffuse thin SAH, with IVH</td>
<td>1-3 Yellow</td>
</tr>
<tr>
<td>III</td>
<td>3 Thick (&gt;1 mm) SAH, no IVH</td>
<td>3-4 Red</td>
</tr>
<tr>
<td>IV</td>
<td>4 Thick SAH with IVH</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Either</td>
<td></td>
</tr>
<tr>
<td>WFNS grading scale</td>
<td>Modified Fisher Scale</td>
<td>VASOGRADE scale</td>
</tr>
<tr>
<td>WFNS</td>
<td>GSC Motor deficit</td>
<td>WFNS</td>
</tr>
<tr>
<td>I</td>
<td>15 Absent</td>
<td>1-2 Green</td>
</tr>
<tr>
<td>II</td>
<td>13 or 14 Present</td>
<td>1-3 Yellow</td>
</tr>
<tr>
<td>III</td>
<td>13 or 14 Present</td>
<td>3-6 Red</td>
</tr>
<tr>
<td>IV</td>
<td>7-12 Either</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>3-6 Either</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GSC, Glasgow Coma Scale; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurological Societies.

and radiologic assessment. Although different approaches exist, the updated guidelines published by the American Heart Association and the Neurocritical Care Society provide valuable evidence-based guidance.

Clinical monitoring consists of repeated neurologic assessment at least every 2 hours to identify new neurologic deficits, deterioration of consciousness indicative of possible ischemia, or an unexpected rise in blood pressure, all of which may indicate DCI. When clinical assessment is not feasible, multimodal monitoring including continuous intracranial EEG, brain tissue oxygen, cerebral blood flow, intracranial pressure (ICP), and microdialysis may be necessary to provide continuous monitoring for complications of vasospasm and DCI.

It is equally important to recognize which patients are at very low risk of developing DCI to make timely decisions regarding reduction in the level of monitoring and prevent adverse effects of prolonged ICU stay, which can also reduce unnecessary cost. In recent studies from different care systems, it was found that patients age 68 or more and those with good clinical and radiological grades at presentation are good candidates for discharge from the ICU soon after aneurysm treatment. These results were incorporated in the VASOGRADE scale—a combination of the WFNS and modified Fisher scale—that was validated in a cohort of 746 patients (Table 1). Patients who are low-risk (ie, VASOGRADE green) may be monitored less aggressively and possibly with only frequent neurologic examination.

Imaging

Ultrasound. Transcranial Doppler ultrasound (TCD) or transcranial color-coded duplex Doppler ultrasound (TCCD) is the preferred primary imaging method for diagnosis and monitoring of vasospasm (Figure 2). Imaging with TCD has many advantages, including portability, availability, and repeatability at the bedside; safety profile (noninvasive and does not require radiation or contrast); immediacy of results for diagnosis in real time; and low cost. Although TCD is an indirect method that cannot measure the exact vessel diameter, it shows narrowing of blood vessels because blood flow velocity accelerates as vessels narrow. In some patients, however, the absence of a temporal bone window (≥ 15% of patients) may make monitoring with TCD unfeasible.

It is important to acquire a baseline TCD measurement on arrival (day 0) and daily thereafter, because TCD can detect vasospasm days before it becomes clinically apparent and thus can aid early intervention with hemodynamic management. Maximum vasospasm is usually detected with TCD after day 7, which can be helpful in planning continued management. After day 12, TCD can document spasm resolution and guide stepping down treatment. Increased resistance (pulsatility index ≥1.2) on TCD is indicative of a possible distal spasm or increased ICP. There are also well-established criteria for using TCD to identify proximal MCA spasm or vertebral and basilar artery vasospasm (Table 2). The diagnostic yield of TCD is higher in the anterior vs posterior circulation and proximal vs distal vessels.

CT and MRI. Single photon emission tomography (SPECT), positron emission tomography (PET), xenon CT, MR perfusion, and CT perfusion have been used in many centers to assess cerebral blood flow and detect perfusion deficits in patients with vasospasm, even in territories remote from constricted large vessels. In recent years, CT angiography (CTA) and CT perfusion (CTP) studies have become the cornerstone of neuroimaging in acute stroke medicine because both provide critical information regarding early ischemia and penumbra. For patients with SAH, however, there are still no randomized trials addressing the efficacy of CTA and CTP for use in diagnosis and patient management. Compared to digital subtraction angiography (DSA), CTA has a high specificity of up to 95%, but tends to overestimate the degree of stenosis. A recent meta-analysis showed that patients with CTP findings indicative of perfusion deficits are approximately 23-fold more likely to experience DCI compared with those with normal CTP results. Thresholds for absolute mean transit time (>5.9 seconds)
Figure 1. Digital subtraction angiography (DSA) of a 48-year old female patient with subarachnoid hemorrhage (SAH) due to rupture of a left posterior communicating artery (PCA) aneurysm (A), which was successfully secured by coiling. On day 3, the patient deteriorated with right side hemiparesis and speech disorders. Subsequent DSA revealed a severe vasospasm (white arrows) of the left middle cerebral artery (MCA) and anterior cerebral artery (ACA) (B). Following angiography, a transluminal angioplasty of the left MCA with balloon hyperglide catheter (black arrow) was performed and nimodipine was infused selectively to both MCA and ACA (C). Two-dimensional DSA at the end of procedure revealed improved vessel diameter of both affected arteries (D). Contributed from the personal archive of Dr. Georgios Magoufis (interventional neuroradiologist).
and cerebral blood flow can distinguish between patients with DCI and clinically stable patients.  

All patients with SAH should undergo CT or MRI imaging (which will serve as a baseline) 24 to 48 hours after aneurysm treatment. Subsequently, a CT, CTA, or CTP should be obtained for every patient if and when they have deterioration on neurologic examination or TCD to determine whether or not urgent intervention is appropriate. Prediction of DCI with CTP on admission has not been proven.

Angiography. Although the criterion standard for detection of vasospasm is DSA, this modality is invasive with the disadvantages of radiation exposure, contrast administration (nephrotoxicity), risk of complications (<1% in experienced centers), and transfer of the patient from intensive care to an angiography suite. These disadvantages may account for the substantial decline in the use of DSA for aneurysmal SAH diagnosis and vasospasm monitoring. In the era of CTA, CTP and TCD, DSA is more likely to be used for patients in whom intervention (balloon angioplasty) is very likely to take place at the same time as angiographic diagnosis of vasospasm.

### Treatment

**Nimodipine**

Oral nimodipine is the only agent approved for DCI prophylaxis. Interestingly, nimodipine does not affect the course of vasospasm but possibly acts through neuroprotection and enhancement of endogenous fibrinolytic activity. A Cochrane review of 16 studies showed that oral nimodipine significantly reduces risk of poor outcome and secondary ischemia after SAH with a number needed to treat (NNT) of 19, although this was not the case for other calcium antagonists or intravenous nimodipine. Oral nimodipine (60 mg every 4 hours) should be started in the emergency department immediately after SAH diagnosis and given for 21 days. The only adverse effect of oral nimodipine is hypotension, which may prove detrimental in the setting of DCI. If hypotension occurs and DCI is present, lower doses more frequently or at the same frequency may be given (30 mg every 2 to 4 hours).

Intraventricular administration of nimodipine microparticles has the theoretical advantage of bypassing systemic adverse effects and acting directly on the target. In the NEWTON study of nimodipine microparticles administered intraventricularly, however, interim analysis failed to reach a statistically significant difference compared to the standard of care and the trial was terminated. No other agents with vasodilating and neuroprotective properties have shown efficacy.

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### Table 2. Transcranial Doppler Criteria for Grading Proximal Middle Cerebral and Basilar Artery Vasospasm

<table>
<thead>
<tr>
<th>MCA vasospasm</th>
<th>Basilar Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MCA vasospasm</strong></td>
<td><strong>MFV, cm/sec</strong></td>
</tr>
<tr>
<td>MFV</td>
<td>MCA/ICA MFV ratio</td>
</tr>
<tr>
<td>&lt;120</td>
<td>≤3</td>
</tr>
<tr>
<td>≥120</td>
<td>5-6</td>
</tr>
<tr>
<td>≥200</td>
<td>≥6</td>
</tr>
<tr>
<td><strong>Basilar Artery</strong></td>
<td></td>
</tr>
<tr>
<td>MFV</td>
<td>BA/EVA MFV ratio</td>
</tr>
<tr>
<td>&gt;70</td>
<td>&gt;2</td>
</tr>
<tr>
<td>&gt;85</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>&gt;85</td>
<td>&gt;3</td>
</tr>
</tbody>
</table>

Abbreviations: BA, basilar artery; EVA, extracranial vertebral artery (at the first cervical level, depth 45-55 mm); ICA, internal carotid artery; MCA, middle cerebral artery; MFV, mean flow velocity; TCD, transcranial Doppler ultrasound.

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A Study of EG-1962 compared to standard of care oral nimodipine in adults with aneurysmal subarachnoid hemorrhage (NCT02790632).
for preventing DCI and improving outcomes. Intravenous magnesium, clazosentan (an endothelin receptor antagonist that effectively reduces vasospasm), and statins have been studied in randomized trials with negative results.

**Hypertension, Hypervolemia, and Hemodilution**

For many years, prophylactic or therapeutic use of induced hypertension, hypervolemia, and hemodilution—triple-H therapy—was the principal approach of restoring impaired cerebral perfusion in patients with DCI after SAH. This was mostly an empiric therapy based on the physiologic rationale related to the hemodynamic consequences of cerebral arterial vasoconstriction. Because vessel diameter is fixed, the only parameters that may effectively increase cerebral blood flow are the mean arterial pressure, blood volume, and blood viscosity (ie, hematocrit). A systematic literature review showed no evidence from controlled trials for a positive effect of triple-H therapy. Of all 3 components of triple-H therapy, only hypertension has the most consistent effect on increasing cerebral blood flow.\(^1\) The HIMALAIA trial\(^2\) was designed to assess the effectiveness of induced hypertension on clinical outcome in patients with DCI, but it was terminated prematurely because of a lack of efficacy on cerebral perfusion and slow recruitment. It was also reported that the early clinical improvement after induced hypertension was counterbalanced by serious adverse events especially in patients with pre-existing cardiopulmonary disease.\(^3\)

In the authors’ current clinical practice, we find it reasonable to treat patients who develop DCI with stepwise blood pressure augmentation and simultaneous neurologic assessment at each mean arterial pressure level, unless cardiac status or unsecured ruptured aneurysm precludes such an approach, in accordance with recent international recommendations. Target blood pressure and choice of vasopressor agents (eg, norepinephrine or phenylephrine) should be individualized according to the patient’s response to treatment and relevant comorbidities. Stepping down hypertensive therapy with simultaneous TCD and neurologic monitoring should be tried after 24 to 48 hours of neurologic improvement.

Because hypervolemia has been linked to poor outcomes, the goal is to maintain a euvoletic state by using isotonic fluids and avoiding fluid overload. Higher hemoglobin levels are associated with better outcomes; however, the appropriate target hemoglobin concentration is unknown. Recommendations of international societies advocate red blood cell transfusion to keep hemoglobin concentration above 8 to 10 mg/dL. A second-line hemodynamic intervention, after optimization of blood pressure, of increasing cardiac output with inotropes is recommended by many centers.

**Endovascular Management**

When hemodynamic management fails to reverse a focal neurologic deficit consistent with vasospasm or is contraindicated, endovascular management is preferred. Prophylactic angioplasty even in patients with high-grade (Fisher grade 3) SAH is not recommended because of a high mortality rate of 8%; this may be due to stretching the target vessel beyond its baseline caliber, which predisposes the vessel to injury (eg, dissection, perforation, and thromboembolism).

In contrast, patients with medically refractory symptomatic vasospasm should be treated with the same urgency as an acute ischemic stroke. Early aggressive treatment with an optimal time window of less than 2 hours is the best strategy to prevent cerebral infarction.\(^4\) Endovascular therapy combines mechanical balloon angioplasty for accessible lesions and vasodilator infusion for distal vessels and microvascular beds. Most experience exists with angioplasty of the proximal vessels (eg, intradural carotid and vertebral artery, basilar artery, M1 segment of middle cerebral artery [MCA], A1 segment of anterior cerebral artery [ACA], or P1 segment of posterior cerebral artery [PCA]); with the development of microcatheter technology, however, distal arterial spasm (A2/A3 segments of ACA, M2 segment of MCA, P2 segment of PCA) can also be accessible. There are numerous case series with a reported success rate of over 90% and a long-lasting result, with only a few patients requiring repetitive interventions.

Different vasodilators have been infused to brain vessels through selective or superselective transarterial catheters, although none has been studied in randomized controlled clinical trials. Papaverine, which was widely used in the past, is no longer used in current practice because of reported neurotoxicity. Nicardipine, verapamil, and to a lesser degree, nimodipine, fasudil, and milrinone are the preferred agents. Intra-arterial infusion can be used as a standalone therapy with the advantages of safety and more diffuse vasodilatory action. Disadvantages of intra-arterial infusion alone are the delayed and short duration of action that may necessitate repetition of the procedure and the possibility of intracranial hypertension and systemic hypotension.

**Summary**

Vasospasm and DCI contribute substantially to mortality and morbidity of patients who experienced SAH. Prevention, effective monitoring, and early detection are the keys to successful management. Close neurologic and TCD monitoring are essential parts of daily care, and CT/CTA/CTP are important for symptomatic patients in danger of cerebral infarction. Oral nimodipine (60 mg every 4 hours) improves neurologic outcomes for patients with vasospasm or DCI. For patients who do not respond to nimodipine, prompt stepwise therapy starting with hemodynamic optimization (euvolemia plus hypertension) progressing to urgent aggressive therapy with balloon angioplasty and infusion of vasodilators may be needed. Because vasospasm is a more complex pathophysiologic

(Continued on page 49)
(Continued from page 41) process than previously understood, more research regarding multimodal approaches and new therapeutic targets is needed.