

REVIEW ARTICLE

Cerebral vasospasm after spontaneous subarachnoid hemorrhage: Pathophysiology, diagnosis, and contemporary management

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Abstract

Cerebral vasospasm (CV) following spontaneous subarachnoid hemorrhage is a serious complication that can lead to delayed cerebral ischemia, significantly increasing both morbidity and mortality. This article offers an in-depth examination of the pathophysiological mechanisms, risk factors, diagnostic strategies, and currently available treatment options concerning CV. Several distinct yet interconnected processes contribute to the development of vasospasm, such as oxidative stress driven by oxyhemoglobin, increased endothelin-1 activity, diminished nitric oxide availability, endothelial dysfunction, vascular inflammation, and sympathetic overactivation. In symptomatic cases, digital subtraction angiography remains the most reliable modality for diagnosis, offering detailed vascular visualization and the opportunity for concurrent therapeutic intervention. Among pharmacological agents, oral nimodipine is the only drug with proven efficacy in enhancing functional outcomes and is strongly endorsed by current clinical guidelines (Class I, Level A). In cases of refractory vasospasm, endovascular treatments such as transluminal balloon angioplasty and intra-arterial vasodilator infusion play a critical role. The management of CV requires an individualized, time-sensitive, and multimodal approach in both diagnosis and therapy. There remains a need for advanced randomized controlled trials and standardized treatment protocols in this field.

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1. Introduction

Spontaneous subarachnoid hemorrhage (sSAH) is a severe cerebrovascular event with high morbidity and mortality, necessitating urgent medical attention. It accounts for approximately 5% of all stroke cases.¹⁻³ The most common etiology of sSAH is the rupture of intracranial aneurysms, which are responsible for about 65% of cases.⁴ Despite advances in the treatment of hypertension and hyperlipidemia and a gradual decline in smoking rates over time, the incidence of sSAH has remained relatively unchanged over the past three decades.⁵ In contrast, significant improvements in surgical and medical management, the widespread availability of neurocritical care units, faster diagnostic tools, and early intervention strategies have led to a nearly 50% reduction

in the mortality rates—which had previously ranged from 32% to 67%—within the last 20 years.^{6–8} Nevertheless, approximately half of the survivors fail to regain their pre-morbid functional status, and one in four patients becomes dependent on others for daily activities.⁸ Moreover, up to 35% of patients report a significant decline in quality of life due to neuropsychiatric sequelae, including memory impairment, depression, anxiety, and post-traumatic stress disorder.^{9–11}

Cerebral vasospasm (CV) and the associated delayed cerebral ischemia (DCI) are among the most frequent and serious complications following sSAH and are closely linked to poor neurological outcomes and prognosis.^{10,12} CV was first described by Ecker and Riemenschneider¹³ in 1951 in association with ruptured intracranial aneurysms, and subsequently, Allcock and Drake¹⁴ demonstrated a significant relationship between CV and focal ischemic neurological symptoms. The incidence of CV after sSAH is reported to be between 30% and 40%, and in 20–30% of these cases, cerebral infarction develops due to DCI.¹⁵ DCI typically occurs between 4 and 12 days after the initial hemorrhage and is defined as a neurological deterioration lasting at least 1 h, unexplained by other causes, including new focal deficits and/or a ≥ 2 -point drop in the Glasgow Coma Scale score.¹⁶

Timely recognition of CV and DCI is critical to preventing irreversible ischemic brain damage.¹⁷ However, diagnosis can be particularly challenging in patients with severe clinical presentations.¹⁸ Currently, no standardized protocol exists that can reliably predict, diagnose early, or effectively treat CV. As a result, a growing body of experimental and clinical research is focused on understanding the pathogenesis of CV through studies investigating genetic predisposition, cellular-level vascular alterations, and underlying molecular mechanisms. For instance, polymorphisms in genes encoding endothelial nitric oxide synthase, haptoglobin, and the endothelin-1 (ET-1) receptor have been linked to an increased risk of vasospasm.^{19–21}

This review aims to provide a comprehensive overview of the pathophysiology, diagnostic strategies, and contemporary treatment modalities of CV following sSAH in light of the current literature.

2. Pathophysiology

Although the exact pathogenesis of CV following sSAH has not been fully elucidated, numerous mechanisms have been proposed, supported by both clinical and experimental evidence. The leading hypothesis suggests that blood and its degradation products entering the subarachnoid space after aneurysmal rupture impair cerebrovascular tone and initiate vasospasm.²²

Fisher *et al.*²³ demonstrated a strong correlation between the amount of subarachnoid blood visible on computed tomography (CT) and the incidence of vasospasm by grading the distribution of blood in the subarachnoid space (Table 1). Particularly, dense blood accumulation in the basal cisterns, the presence of intraventricular hemorrhage, and delayed clearance of blood are associated with a significantly increased risk of vasospasm. Similarly, a higher Hunt and Hess grade at admission is proportionally related to the likelihood of vasospasm (Table 1).²⁴

The extravasated blood in the subarachnoid space contributes to early ischemic injury by increasing intracranial pressure, disrupting cerebrospinal fluid (CSF) circulation, and reducing cerebral perfusion pressure.²⁸ The initial 72-h post-hemorrhage period—often termed early brain injury—is now recognized as a critical phase during which global cerebral ischemia, blood–brain barrier disruption, and cell death occur, setting the stage for subsequent vasospasm and DCI.^{8,29} Among the degradation products, oxyhemoglobin and ferrous hemoglobin play pivotal roles in initiating secondary processes such as oxidative stress, inflammation, and endothelial injury, which collectively predispose to CV, DCI, and cerebral infarction.^{28,30}

One key mechanism involves the generation of reactive oxygen species (ROS), resulting from mitochondrial dysfunction and hemoglobin degradation. These radicals induce lipid peroxidation and increase intracellular calcium, leading to endothelial damage and enhanced vasoconstriction.^{31–33} Simultaneously, ROS inhibits endothelial nitric oxide synthase, while hemoglobin accumulated in the CSF binds nitric oxide, reducing its bioavailability.^{34,35} The reduction in nitric oxide levels contributes to microthrombosis, arteriolar narrowing, and neuronal apoptosis.³⁶

ET-1, a potent vasoconstrictor found at significantly elevated levels in the CSF after sSAH, is strongly associated with vasospasm development.³⁷ Its release is stimulated by inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF- α), and it also promotes vascular smooth muscle cell inflammation and proliferation.³⁸ The vascular endothelium regulates various physiological processes, including vascular tone, coagulation, cell adhesion, and inflammation. Endothelial dysfunction leads to loss of this regulatory balance, resulting in platelet aggregation and exaggerated smooth muscle cell contractility, both of which contribute to vasospasm.³⁹ On a molecular level, increased ET-1 levels promote vasoconstriction by enhancing inflammatory gene expression and calcium channel activation.⁴⁰

Cerebral arteries undergo a biphasic vasospastic response following sSAH. The initial phase begins within

Table 1. Grading scales for spontaneous subarachnoid hemorrhage

Grade	Clinical assessment		Radiologic assessment
	Hunt and Hess scale ²⁵	WFNS scale ²⁶	Modified Fisher scale ²⁷
0	No clinical symptoms	-	No SAH, no IVH
1	Mild headache, nuchal rigidity, or asymptomatic	GCS 15	Thin SAH, no IVH
2	Moderate to severe headache, nuchal rigidity, cranial nerve palsy	GCS 13–14, no motor deficit	Thin SAH, IVH present
3	Confusion, lethargy, mild focal neurological deficits	GCS 13–14, motor deficit present	Thick SAH, no IVH
4	Stupor, severe focal neurological deficits	GCS 7–12	Thick SAH, IVH present
5	Coma, decerebrate or decorticate posturing	GCS 3–6	-

Abbreviations: GCS: Glasgow coma scale; IVH: Intraventricular hemorrhage; SAH: Subarachnoid hemorrhage; WFNS: World Federation of Neurosurgical Societies.

minutes and lasts up to 6 h, whereas the secondary phase may involve both pial and intraparenchymal vessels and persists for up to 24 h.^{41–43} This process is accompanied by inflammatory cell infiltration, increased ET release, and disruption of the blood-brain barrier. Accumulation of inflammatory cells in the subarachnoid space leads to the release of ET-1, ROS, and other toxic metabolites into the CSF, exacerbating microcirculatory disturbances and deepening ischemic injury.^{44,45}

Infiltrating neutrophils exacerbate vasospasm by releasing ROS (*e.g.*, through myeloperoxidase), and activated microglia—via Toll-like receptor 4 signaling—secrete proinflammatory cytokines such as TNF- α , compounding endothelial injury and vasoconstriction.^{46–49} Moreover, DCI is now understood to sometimes occur even without angiographic vasospasm; recent evidence implicates cortical spreading depolarizations triggered by subarachnoid blood in causing microcirculatory dysfunction through waves of neuronal depolarization that induce neuroinflammation, microthrombosis, and focal vasoconstriction.^{50,51}

In addition, excessive activation of the sympathetic nervous system following sSAH plays a significant role in vasospasm development. Elevated catecholamine levels stimulate α -1 adrenergic receptors, enhancing vasoconstriction.^{52,53} ROS-mediated suppression of endothelium-derived relaxation mechanisms further disrupts intracellular signaling, impairing endothelial functions critical for vasodilation, inflammation modulation, and hemostasis.^{54,55}

In summary, the development of CV results from the interplay of multiple interrelated pathophysiological mechanisms, including oxidative stress, nitric oxide deficiency, ET elevation, inflammation, endothelial dysfunction, and sympathetic hyperactivity. This multifactorial nature underscores the limitations of monotherapeutic approaches and highlights the need for multimodal treatment strategies.

3. Risk factors

The risk factors contributing to CV are multifactorial and encompass demographic characteristics, clinical and laboratory findings, imaging features, and behavioral habits (Table 2).

Younger age and female sex have been identified as significant predisposing variables for CV.^{57,66} Notably, women younger than 55 years exhibit a significantly higher incidence of vasospasm.⁵⁶ Smoking and alcohol consumption have been consistently associated with an increased risk of CV across multiple studies.^{58,59} Additionally, the use of cannabis and cocaine has been reported as a potential risk enhancer in some investigations.⁵⁷

The risk of vasospasm can be predicted using clinical grading systems. Patients with a modified Fisher score ≥ 3 are at significantly higher risk due to the increased volume of subarachnoid blood.⁵⁹ Similarly, individuals presenting with a Hunt and Hess score $\geq \text{II}$ have a greater likelihood of developing vasospasm due to their compromised neurological status.⁵⁷ Comorbidities such as congestive heart failure, hypertension, diabetes mellitus, and a prior history of stroke have also been found to be significantly associated with CV development.⁶⁰

Among the laboratory parameters used to predict CV risk are common biomarkers such as leukocytosis, hyponatremia, hypokalemia, hypoalbuminemia, and anemia.⁵⁷ Elevated leukocyte count has been identified as an independent predictor of CV, reflecting a systemic inflammatory response. In addition, increased levels of inflammatory and metabolic markers, including C-reactive protein, procalcitonin, von Willebrand factor, vascular endothelial growth factor, and the glucose-to-potassium ratio, have also been correlated with CV.^{61–63}

Radiological features associated with an increased risk of CV include internal carotid artery aneurysms, arterial

Table 2. Risk factors for cerebral vasospasm after spontaneous subarachnoid hemorrhage

Risk factor category	Specific risk factors	Notes
Demographic factors	• Younger age • Female sex	Particularly significant in females <55 years ⁵⁶
Behavioral factors	• Smoking • Alcohol consumption • Cannabis/Cocaine use	Modifiable risk factors associated with increased CV incidence ⁵⁷⁻⁵⁹
Clinical and radiological severity scores	• Modified Fisher score ≥3 • Hunt and Hess grade ≥II	Higher initial severity correlates with higher CV risk ^{53,57}
Comorbid conditions	• Hypertension • Congestive heart failure • Diabetes mellitus • History of stroke	Associated with increased vulnerability to CV ⁶⁰
Laboratory findings	• Leukocytosis • Hypoalbuminemia • Hyponatremia • Hypokalemia • Anemia	Inflammatory and metabolic indicators of elevated CV risk ^{57,61-63}
Radiologic characteristics	• Large subarachnoid clot burden • Intraventricular hemorrhage • Internal carotid artery aneurysms • Arterial tortuosity and complex aneurysm morphology	High clot burden and complex vascular anatomy increase CV probability ^{64,65}
Procedural factors	Endovascular coiling (vs. surgical clipping)	Some studies suggest higher CV risk after coiling ⁶⁰

Abbreviation: CV: Cerebral vasospasm.

tortuosity, and complex aneurysmal morphologies.^{64,65} Furthermore, some studies have reported that endovascular coiling may confer a higher risk of CV compared to surgical clipping.⁶⁰

The development of CV results from the interplay of both modifiable (e.g., smoking, hypertension, hypovolemia) and non-modifiable (e.g., age, sex) risk factors. In this context, careful clinical assessment of these variables is essential for the development of individualized monitoring and treatment strategies.

4. Clinical diagnosis

Early recognition of CV is critical for preventing complications following sSAH. The period of highest risk for vasospasm typically falls between days 4 and 14 after hemorrhage, with clinical symptoms most frequently emerging between days 6 and 8.⁶⁷ During this time, close and regular neurological examinations serve as a fundamental tool for the timely detection of CV. In the literature, digital subtraction angiography performed

around day 7 post-sSAH reveals angiographic vasospasm in approximately 20% to 100% of cases; however, only about 30% of these patients exhibit accompanying clinical symptoms.⁶⁸

The Glasgow coma scale (GCS) is widely used to assess consciousness and scores patients from 3 to 15 based on three parameters: Eye opening, verbal response, and best motor response. Clinical deterioration is typically defined as a reduction of at least two points in the GCS score.⁶⁹ Although originally developed for the objective assessment of traumatic brain injury, the GCS is also widely used in sSAH patients for initial prognostication and subsequent monitoring.

However, the GCS has certain limitations. The verbal response component cannot be assessed in intubated patients, and the reliance on only the best motor response may lead to underrecognition of lateralized motor deficits such as hemiparesis. To address these shortcomings, the World Federation of Neurological Surgeons (WFNS) scale was developed, incorporating motor deficits into the assessment (Table 1).⁷⁰ Although the WFNS score offers a more comprehensive evaluation of neurological status at presentation, it has limited utility in tracking clinical changes over time.

It is also important to note that late neurological deterioration following sSAH is not always attributable to vasospasm. Conditions such as cerebral edema, rebleeding, acute hydrocephalus, sepsis, hyponatremia, hypotension, and hypoxia can all mimic the clinical presentation of CV. Therefore, a careful differential diagnosis must be conducted before confirming CV.⁷¹

5. Radiological diagnosis

Radiological modalities play a pivotal role in the diagnosis of CV following spontaneous sSAH, particularly when supported by clinical findings, as they aid in differential diagnosis and treatment planning (Table 3). Imaging and physiological monitoring techniques enable the assessment not only of anatomical vessel narrowing but also of alterations in cerebral perfusion.

Digital subtraction angiography (DSA) is considered the gold standard for diagnosing CV due to its invasive nature and ability to dynamically visualize vascular anatomy with high resolution. It allows evaluation of distal vessel segments and offers the opportunity for simultaneous endovascular interventions.^{8,72} The severity of vasospasm is classified based on segmental distribution, asymmetry compared to the contralateral side, and the percentage of luminal narrowing: >50% is considered severe, 25–50% moderate, and <25% mild.¹⁰² However, due to its

Table 3. Radiological and physiological diagnostic modalities for cerebral vasospasm after spontaneous subarachnoid hemorrhage

Modality	Diagnostic role	Sensitivity/ specificity	Advantages	Limitations
Digital subtraction angiography ^{8,72-74}	Gold standard for CV diagnosis; evaluates vessel narrowing dynamically.	100/100	High-resolution imaging; assessment of distal vessels; allows for simultaneous endovascular treatment.	Invasive; neurological complication risk (1.3–2.4%); used mainly in symptomatic patients or treatment planning.
Computed tomography angiography ⁷⁵	Detects proximal large-vessel vasospasm; evaluates vessel narrowing.	79.6/93.1	High sensitivity and specificity; non-invasive; widely available.	May overestimate severity of stenosis; limited in distal vessel assessment.
Computed tomography perfusion ^{76,77}	Assesses hemodynamic impact of CV; detects hypoperfusion.	74.1/93.0	Provides quantitative evaluation of cerebral perfusion parameters (CBF, CBV, MTT, and TTP).	Radiation exposure; requires contrast agent; patient-specific considerations necessary.
Transcranial Doppler Ultrasound ⁷⁸⁻⁸¹	Non-invasive monitoring of flow velocities in major vessels (e.g., MCA, basilar artery).	67/99 (MCA)	Bedside applicability; serial monitoring possible; non-invasive.	Limited ability to evaluate distal vessels; operator-dependent; moderate sensitivity (44–79%).
Magnetic resonance angiography ⁸²	Non-invasive assessment of cerebral vessels without ionizing radiation or contrast.	91/98	Useful in selected cases; no radiation exposure.	Limited spatial resolution; hemodynamic artifacts; less reliable for distal or low-flow regions.
Diffusion-weighted MRI ⁸³⁻⁸⁵	Detects early ischemic injury associated with CV; prognostic value.	Not validated	High sensitivity for cytotoxic edema and silent infarcts; identifies small cortical lesions undetectable by other methods.	Limited availability in emergency settings; cannot directly visualize vasospasm.
Electroencephalography ^{86,87}	Early detection of cortical ischemia secondary to CV.	89/84	Bedside application; high sensitivity and specificity when using parameters like alpha/delta ratio.	Affected by sedation, metabolic disturbances; non-specific findings; requires expert interpretation.
Xenon-enhanced computed tomography ⁸⁸⁻⁹⁰	Direct measurement of rCBF.	Not validated	High accuracy for assessing hypoperfusion.	Requires specialized equipment; limited to point-in-time measurement; potential side effects (e.g., headache, nausea).
Single-photon emission computed tomography ⁹¹⁻⁹³	Evaluates regional cerebral perfusion independently of cause.	89/75	Whole-brain imaging possible; useful adjunctive tool.	Low spatial resolution; high cost; radioactive exposure; not ideal for acute settings.
Near-infrared spectroscopy ⁹⁴⁻⁹⁶	Monitors cortical oxygen saturation changes associated with hypoperfusion.	86/86	Continuous, non-invasive bedside monitoring.	Limited penetration depth; only evaluates superficial cortical regions.
Microdialysis ^{69,97,98}	Measures extracellular metabolic markers indicating ischemia (e.g., lactate/pyruvate ratio, glutamate).	94/88	High sensitivity and specificity for ischemic changes; allows real-time biochemical monitoring.	Invasive; risk of hematoma, infection; limited to the local tissue environment.
Jugular blood sampling ⁹⁹⁻¹⁰¹	Assesses global cerebral oxygenation and arteriovenous oxygen differences.	Not validated	Continuous monitoring of cerebral oxygen balance; predictive of hypoperfusion and hyperemia.	Invasive; reflects global rather than regional changes; catheter-associated risks.

Abbreviations: CBF: Cerebral blood flow; CBV: Cerebral blood volume; CV: Cerebral vasospasm; MCA: Middle cerebral artery; MRI: Magnetic resonance imaging; MTT: Mean transit time; rCBF: Regional cerebral blood flow; TTP: Time to peak.

invasiveness and a reported neurological complication rate of approximately 1.3–2.4%, DSA is generally reserved for symptomatic patients or those undergoing interventional procedures.^{73,74}

Computed tomography angiography (CTA) provides high sensitivity and specificity for detecting proximal large-vessel vasospasm. With advanced reconstruction

techniques, the branches of the circle of Willis can be assessed and graded: <30% narrowing is considered mild, 30–60% moderate, and >60% severe.⁷⁵ Nevertheless, overestimation of stenosis is a known limitation that requires cautious interpretation.¹⁰³

CT perfusion is a functional imaging modality that assesses hemodynamic changes following vasospasm.

Parameters such as cerebral blood flow (CBF), cerebral blood volume, mean transit time, and time to peak can quantitatively identify hypoperfused regions. Significant alterations in these parameters have been observed in vascular territories with >50% narrowing, demonstrating a direct relationship between the severity of vasospasm and perfusion deficits.^{76,77} However, its use must be individualized due to limitations such as radiation exposure and contrast medium requirements.

Transcranial Doppler ultrasound (TCD) provides an indirect, non-invasive assessment of CV by measuring blood flow velocities in major cerebral arteries such as the middle cerebral artery (MCA) and basilar artery. A mean flow velocity >120 cm/s in the MCA and a Lindegaard ratio >3 are suggestive of vasospasm.^{78,79} Progressive velocity increases, particularly exceeding 200 cm/s, are highly specific indicators of severe CV. Reported sensitivity and specificity of TCD range from 44% to 79% and from 80% and 100%, respectively.^{80,81} While it is advantageous for serial bedside monitoring due to its repeatability and non-invasiveness, it lacks utility in evaluating distal vessels.

Magnetic resonance angiography (MRA) offers a non-invasive method for evaluating cerebral vasculature without requiring contrast or ionizing radiation. However, due to its flow-dependence, MRA primarily reflects hemodynamic changes rather than anatomical details, reducing its sensitivity for detecting low-flow or distal vasospasm. Compared to DSA and CTA, its spatial resolution is lower, and artifacts from methemoglobin or surgical clips, and limited emergency accessibility, further restrict its clinical utility.^{82,104} Thus, while MRA serves as a complementary tool, it does not replace conventional angiography in CV management.

Diffusion-weighted magnetic resonance imaging (DWI-MRI) is a highly sensitive modality for detecting cerebral ischemia following sSAH, especially delayed ischemic changes secondary to vasospasm.^{83,84} Lesions detected within the first 72 h reflect early brain injury and may have prognostic value for later DCI. Cytotoxic edema and infarcts secondary to vasospasm are characterized by hyperintensity on DWI and corresponding reduction in apparent diffusion coefficient values.¹⁰⁵ In contrast, vasogenic edema shows increased DWI signal but normal apparent diffusion coefficient. DWI-MRI can also reveal small cortical infarcts and silent ischemic areas undetectable by conventional techniques, making it a valuable complementary method for early diagnosis and monitoring of CV-related ischemia.⁸⁵

Electroencephalography (EEG) is a non-invasive, bedside monitoring tool capable of detecting cortical ischemia secondary to CV in the early phase. Decreases

in parameters such as the alpha/delta ratio are associated with high sensitivity and specificity for predicting delayed ischemic neurological deficits.⁸⁶ However, EEG patterns can be influenced by sedation, metabolic disorders, hydrocephalus, or rebleeding, limiting its specificity.⁸⁷ Interpretation requires expertise and should be supported by continuous monitoring, making EEG a useful adjunct rather than a standalone diagnostic tool.

Xenon-enhanced CT is a reliable method for directly measuring regional cerebral blood flow (rCBF) by detecting hypoperfusion due to CV. It relies on the distribution of radiopaque, diffusible xenon gas—administered intravenously or via inhalation—based on blood flow to brain tissue. Despite its accuracy, clinical utility is limited by the requirement for specialized equipment, patient cooperation, and the ability to capture only momentary perfusion data.⁸⁸ Side effects such as headache, nausea, vomiting, respiratory depression, and seizures have also been reported.^{89,90}

Single-photon emission computed tomography (SPECT) assesses rCBF based on the uptake of radioactive tracers such as technetium-99m hexamethyl propylene amine oxime (Tc-99m HMPAO) during cerebral microcirculation.^{91,92} A major advantage is its ability to detect hypoperfusion regardless of the underlying cause. Although it provides whole-brain imaging, spatial resolution is limited. Compared to DSA, SPECT has a sensitivity of 89% and a specificity of 75%.¹⁰⁶ However, its use in emergency settings is limited due to high cost, radiation exposure, and long acquisition times.⁹³

Near-infrared spectroscopy (NIRS) measures changes in cortical deoxyhemoglobin to detect drops in oxygen saturation. It enables continuous, non-invasive monitoring.^{94,95} Decreased oxygenation during vasospasm can trigger further investigation.⁹⁶ However, NIRS is limited by its superficial depth of penetration and lower clinical sensitivity.

Microdialysis involves the intracranial placement of microcatheters to monitor extracellular levels of metabolic markers such as glucose, lactate, pyruvate, glutamate, and glycerol. Increases in lactate/pyruvate ratios and elevated glutamate or glycerol levels are indicative of ischemic stress. Sensitivity and specificity may reach up to 89% and 82%, respectively.^{97,98} However, its invasiveness, risk of hematoma or infection, potential probe malfunction, and placement errors restrict its widespread use.⁶⁹

Jugular bulb oximetry provides continuous monitoring of cerebral oxygenation via a fiber-optic catheter inserted into the internal jugular bulb under ultrasound or fluoroscopic guidance. Parameters such as PO₂, PCO₂, pH, and temperature are measured, and arterio-jugular differences in oxygen content (AJDO₂) are calculated.

A jugular venous oxygen saturation (SjvO_2) <55% suggests cerebral ischemia, whereas levels >75% may indicate hyperemia.⁹⁹ Continuous monitoring can help predict poor oxygenation and neurological deterioration in sSAH patients.^{100,101} However, it is invasive and reflects global oxygenation rather than regional changes, limiting its

utility in detecting focal vasospasm.

6. Medical treatment

Various pharmacological and supportive treatment strategies have been developed to prevent and manage

Table 4. Medical treatment strategies for cerebral vasospasm after spontaneous subarachnoid hemorrhage

Therapy	Mechanism/target	Evidence/effectiveness	Limitations/comments
Triple-H therapy (hypervolemia, hemodilution, hypertension) ^{8,107-111}	Augment cerebral perfusion.	Current guidelines recommend maintaining euvolemia and inducing hypertension only in symptomatic patients.	Hypervolemia and hemodilution increase the risk of complications (e.g., pulmonary edema, myocardial ischemia).
Nimodipine ^{8,12,112,113}	L-type calcium channel blocker; neuroprotective.	Strong evidence (Class I, level A); reduces DCI incidence and improves outcomes.	Risk of hypotension; IV route reserved for patients unable to tolerate enteral administration.
Magnesium sulfate ¹¹⁴⁻¹¹⁶	NMDA receptor inhibition; calcium channel blockade.	No significant benefit shown in large phase III trials (IMASH, MASH-2).	Not routinely recommended.
Statins ¹¹⁷⁻¹²¹	Improve endothelial function; increase nitric oxide synthesis.	Conflicting evidence; STASH trial showed no significant benefit on clinical outcomes.	Not currently recommended for routine prophylactic use.
Endothelin-1 receptor antagonists (e.g., clazosentan) ¹²²⁻¹²⁵	Block vasoconstrictive effects of ET-1.	Reduced angiographic vasospasm (CONSCIOUS-1); clinical benefits remain inconsistent (CONSCIOUS-2, -3).	Associated with adverse effects (hypotension, pulmonary edema, anemia).
Corticosteroids ¹²⁶	Anti-inflammatory and electrolyte-stabilizing effects.	Some reduction in DCI incidence; no proven improvement in neurological outcomes.	Low-quality evidence; further studies required.
Milrinone ¹²⁷⁻¹³⁰	PDE-3 inhibitor; promotes vasodilation and anti-inflammation.	Promising in retrospective studies and case series (e.g., Montreal protocol).	Hypotension and tachycardia are notable adverse effects; data are limited.
Nicardipine ¹²²⁻¹²⁵	Dihydropyridine calcium channel blocker.	Intra-arterial cisternal administration showed benefit; intravenous use was not superior to nimodipine.	Mainly, adjunctive use is considered.
Cilostazol ¹³¹⁻¹³³	PDE-3 inhibitor; vasodilation and anti-thrombotic effects.	Meta-analyses suggest a reduction in symptomatic vasospasm and infarction risk.	Clinical results are mixed; there is no standard practice yet.
Fasudil ¹³⁴⁻¹³⁶	Rho-kinase inhibitor; reduces vascular contraction and inflammation.	Widely used in Japan; meta-analyses show reduced CV and improved outcomes.	Considered adjunct to nimodipine; broader validation needed.
Sildenafil ^{137,138}	PDE-5 inhibitor; promotes cerebral vasodilation.	Beneficial effects in animal models.	Human data limited; further trials required.
Nitric oxide donors ¹³⁹⁻¹⁴²	Increase nitric oxide levels for vasodilation.	Effective in pre-clinical models.	Hypotension and systemic toxicity limit clinical use.
Erythropoietin ^{143,144}	Neuroprotective; enhances cerebral oxygenation.	Some small case series reports improved tissue oxygenation.	Mechanism unclear; evidence limited.
Anticoagulants (e.g., low-dose heparin) ¹⁴⁵⁻¹⁴⁷	Potentially reduce CV incidence.	Conflicting evidence; hemorrhagic complications remain a concern.	Not routinely recommended.
CSF drainage (lumbar drain) ^{148,149}	Removes subarachnoid blood; reduces intracranial pressure.	Shown to reduce CV and poor outcomes.	Requires careful monitoring to avoid overdrainage complications.
Cisternal irrigation ¹⁵⁰	Washes out subarachnoid clot burden intraoperatively.	May reduce angiographic CV and DCI risk.	Limited to selected surgical cases.
Intrathecal administration (e.g., nimodipine, milrinone) ^{151,152}	Direct pharmacological effect on vessels exposed to blood.	Early studies show potential benefits.	More prospective trials are needed.

Abbreviations: CSF: Cerebrospinal fluid; CV: Cerebral vasospasm; DCI: Delayed cerebral ischemia; ET-1: Endothelin-1; NMDA: N-methyl-D-aspartate; PDE: Phosphodiesterase.

delayed ischemic injury associated with CV following sSAH (Table 4). Current approaches focus on preserving cerebral perfusion, suppressing vasoconstrictive responses, and minimizing neuronal damage.

Triple-H therapy (hypervolemia, hemodilution, and hypertension), historically used to address CV-related perfusion deficits, has recently come under scrutiny. Randomized trials have demonstrated that hypervolemia and hemodilution are associated with significant complications—such as pulmonary edema, hyponatremia, and myocardial ischemia—and do not significantly improve clinical outcomes.¹⁰⁷⁻¹¹¹ Accordingly, modern practice has largely abandoned prophylactic triple-H therapy; current guidelines emphasize maintaining euvolemia and using induced hypertension primarily for patients with neurologic deterioration due to DCI.^{8,153}

Nimodipine, a dihydropyridine L-type calcium channel blocker, remains the only pharmacologic agent with demonstrated efficacy in reducing DCI and improving neurological outcomes following sSAH. It is strongly recommended with Class I, level A evidence in current guidelines.⁸ The standard dose is 60 mg orally every 4–6 h. While the exact mechanism remains unclear, potential effects include reduced intracellular calcium levels, selective relaxation of cerebral vascular smooth muscle, and enhanced collateral flow through small vessels.¹² Intravenous administration should be reserved for cases where enteral delivery is not feasible.^{8,112} Hypotension is the most frequently reported side effect, requiring cautious dose titration—particularly in hemodynamically unstable patients—and is more pronounced with intravenous use.¹¹³

Magnesium sulfate aims to promote vasodilation and reduce excitotoxicity via N-methyl-D-aspartate (NMDA) receptor inhibition and voltage-gated calcium channel blockade.¹¹⁴ However, phase III multicenter trials such as IMASH and MASH-2 failed to demonstrate benefits on CV or DCI.^{115,116}

Statins have the potential to enhance endothelial function and increase nitric oxide synthesis.¹¹⁷ Although some meta-analyses have reported reductions in vasospasm incidence, their effects on mortality and neurological outcomes remain inconsistent.¹¹⁸⁻¹²⁰ Major phase III trials, including STASH, failed to provide sufficient evidence to support routine prophylactic use.^{117,121}

ET-1 receptor antagonists aim to inhibit the potent vasoconstrictive effects of elevated ET-1 levels following sSAH. Clazosentan was shown in the CONSCIOUS-1 trial to reduce angiographic vasospasm in a dose-dependent manner. However, CONSCIOUS-2 and -3 failed to demonstrate clinical benefit and reported significant

adverse events such as hypotension, pulmonary edema, and anemia.¹²²⁻¹²⁴ Consequently, CONSCIOUS-3 was terminated early. In contrast, two recent Japanese phase III trials (JapicCTI-163368 and JapicCTI-163369) reported significant reductions in vasospasm, delayed ischemic neurological deficits, and ischemic symptoms with clazosentan.¹²⁵ As a result of these findings, clazosentan was approved in Japan in early 2022 for vasospasm prophylaxis after aneurysmal subarachnoid hemorrhage, although it remains unapproved elsewhere pending further evidence of clinical benefits.¹⁵⁴ Nonetheless, a large meta-analysis found no significant effect on mortality or functional recovery.¹⁵⁵

Corticosteroids, owing to their anti-inflammatory and electrolyte-balancing properties, may theoretically be beneficial. While some studies suggest a reduction in DCI incidence, consistent improvements in neurological outcomes have not been demonstrated, and available data are methodologically heterogeneous and low in quality. Well-designed randomized trials are required to clarify their efficacy.¹²⁶

Milrinone, a phosphodiesterase-3 inhibitor, increases intracellular cAMP, promoting vasodilation and exerting anti-inflammatory effects. It can be administered intravenously or intra-arterially during endovascular procedures in cases of refractory CV.¹²⁷ The Montreal Neurological Hospital protocol reported good tolerance and favorable outcomes with intravenous infusion.¹⁵⁶ However, current data are primarily based on retrospective studies and systematic reviews. Main side effects include systemic hypotension and tachycardia.¹²⁹⁻¹³¹

Nicardipine, another dihydropyridine calcium channel blocker, has demonstrated efficacy via intravenous infusion in treating CV and DCI.^{157,158} Although not proven superior to nimodipine in Cochrane reviews, intraoperative cisternal administration showed significant benefit in a phase II randomized trial.^{159,160}

Cilostazol exerts vasodilatory effects through phosphodiesterase-3 inhibition and reduces microemboli formation by inhibiting platelet aggregation.¹³¹ Multicenter randomized trials have shown reduced angiographic CV incidence, but clinical outcome effects have been inconsistent.¹³² Nevertheless, meta-analyses have reported reduced risk of symptomatic vasospasm, infarction, and poor outcomes, positioning cilostazol as a promising and safe agent, though not yet widely adopted in clinical practice.¹³³

Fasudil, a Rho-kinase inhibitor that reduces smooth muscle contractility and vascular inflammation, is used in Japan for CV prophylaxis.¹³⁴ Meta-analyses and large series have demonstrated significant reductions in CV and DCI incidence and improved clinical outcomes.^{135,136} Addition

to nimodipine has been associated with better clinical results.¹³⁴

Sildenafil, a phosphodiesterase-5 inhibitor, promotes vasodilation in cerebral arteries. Although it significantly increases vessel diameter in animal models, clinical data in humans remain limited, and further investigation is warranted.^{137,138}

Nitric oxide donors—such as sodium nitroprusside, proanthocyanidin, and nebivolol—aim to enhance nitric oxide-mediated vasodilation. While effective in increasing CBF in animal models, side effects such as hypotension, reduced perfusion pressure, and systemic toxicity significantly limit their clinical application.¹³⁹⁻¹⁴²

Erythropoietin has shown potential to improve cerebral oxygenation and provide neuroprotection, with some case series reporting increased tissue oxygenation hours after administration.¹⁴³ However, its mechanisms remain unclear, and supporting evidence is limited.¹⁴⁴

Anticoagulants, particularly low-dose heparin, have been investigated for reducing CV incidence. Current data remain conflicting regarding efficacy, and the risk of hemorrhagic complications precludes routine clinical use.¹⁴⁵⁻¹⁴⁷

Efforts to remove subarachnoid blood, which plays a key role in CV pathophysiology, offer complementary benefits to pharmacologic treatment. Lumbar drainage (LD), by reducing intracranial pressure and clearing hemorrhagic material from cisternal spaces, may reduce symptomatic vasospasm, secondary infarction, and early mortality.^{148,149} Recent meta-analyses support significant reductions in these complications among LD-treated patients.¹⁶¹ Furthermore, LD helps maintain physiologic CSF flow, facilitating gravitational removal of spasmogenic substances from spinal cisterns and contributing to intracranial pressure regulation. However, data on its effect on functional recovery are inconsistent—likely due to the multifactorial nature of neurological outcomes. Serial lumbar puncture has shown comparable clinical efficacy with a lower risk of CSF infection, suggesting it as a viable alternative in selected cases.¹⁶² LD should thus be considered an effective option for vasospasm prophylaxis and ischemia risk reduction in carefully selected patients, based on individual risk-benefit assessment.

Intraoperative or post-operative cisternal irrigation may mechanically remove intracranial hematoma, potentially reducing angiographic vasospasm and DCI.¹⁵⁰ Additionally, intrathecal administration of agents such as nimodipine or milrinone in selected cases may exert direct pharmacologic effects on subarachnoid vascular segments to prevent vasospasm. While supported by a limited

number of prospective studies, these interventions merit consideration due to their potential benefits.^{151,152}

7. Endovascular treatment

In the management of CV following sSAH, endovascular interventions play a crucial role in cases refractory to medical therapy (Table 5). The most commonly used endovascular modalities in this context are transluminal balloon angioplasty (TBA) and intra-arterial vasodilator infusions.

TBA is particularly effective in large-caliber proximal vessel segments. It exerts its therapeutic effect by mechanically reducing smooth muscle tone in the vessel wall, resulting in prolonged dilation.¹⁶³ Studies using both compliant and non-compliant balloons have reported comparable success rates, and restoration of normal or supranormal vessel diameter after the initial angioplasty has been associated with reduced recurrence rates.¹⁶⁴ However, due to its applicability being limited to large vessels and the potential risk of complications, prophylactic use is not recommended.¹⁶⁵

Intra-arterial vasodilators are more effective in distal and smaller-caliber vessels, and they carry a lower risk of mechanical trauma. Agents such as nimodipine, verapamil, and milrinone are frequently employed. In particular, the combination of milrinone and nimodipine has been found effective as a rescue therapy in refractory vasospasm cases.¹⁶⁶ Conversely, intra-arterial papaverine has largely fallen out of favor due to adverse effects such as increased intracranial pressure and reduced cerebral oxygenation.^{163,167,168}

A relatively novel technique, stent-retriever angioplasty, utilizes self-expanding, retrievable stents. This method minimizes endothelial injury, offers short procedure times, and allows maintenance of distal perfusion. Additionally, it permits simultaneous intra-arterial vasodilator infusion, potentially enhancing therapeutic efficacy.¹⁶⁹ However, limited radial force may result in insufficient dilation in some cases, and further clinical studies are needed to validate its efficacy.¹⁷⁰ Notwithstanding its theoretical endothelial preservation, manipulating friable, vasospastic segments with a stent-retriever may still entail risks of endothelial injury, dissection, or even perforation; meticulous patient/segment selection and gentle technique are essential.^{171,172} Moreover, the current evidence base largely consists of small case series and retrospective cohorts; prospective multicenter evaluations are required to define safety, indications, and comparative effectiveness versus TBA and intra-arterial vasodilator infusion.^{171,173}

The combination of intra-arterial vasodilator infusion

Table 5. Endovascular treatment strategies for cerebral vasospasm after spontaneous subarachnoid hemorrhage

Endovascular technique	Mechanism/target	Advantages	Limitations/comments
TBA ¹⁶³⁻¹⁶⁶	Mechanical dilation of proximal large-caliber vessels; reduces smooth muscle tone.	Provides durable vessel dilation; effective for major arteries; reduces recurrence if achieving normal or supranormal diameter.	Limited to large vessels; invasive; potential complications; not recommended for prophylactic use.
Intra-arterial vasodilator infusion ^{163,166-168}	Pharmacological vasodilation, effective in smaller vessels.	Lower mechanical trauma risk; multiple agents available (nimodipine, verapamil, milrinone); combination therapy is effective.	Temporary effect; repeated treatments often necessary; papaverine use largely abandoned due to adverse effects (ICP elevation, decreased oxygenation).
Stent-retriever angioplasty ^{169,170}	Mechanical vessel expansion using self-expanding retrievable stents; minimal endothelial damage.	Short procedure time; maintenance of distal perfusion; possibility of simultaneous intra-arterial vasodilator infusion.	Lower radial force may cause insufficient dilation in some cases; it requires further validation by clinical trials.
Combination therapy (TBA+intra-arterial vasodilators) ¹⁷¹⁻¹⁷³	Address both proximal and distal vessel narrowing simultaneously.	May improve rescue outcomes in refractory vasospasm; superior functional outcomes compared to medical therapy alone.	Increased radiation exposure; higher procedural cost; potential need for multiple interventions.

Abbreviations: ICP: Intracranial pressure; TBA: Transluminal balloon angioplasty.

and TBA may be effective for both proximal and distal vessel segments.¹⁷⁴ It has shown promise as a salvage therapy in refractory cases; however, potential drawbacks such as increased radiation exposure and higher costs must be considered.^{175,176}

Meta-analyses have reported better functional outcomes and lower mortality rates in patients treated with endovascular interventions compared to those receiving medical therapy alone.¹⁷⁷ Nonetheless, repeated procedures may be required, which can prolong intensive care unit (ICU) stays and increase the risk of complications.

From a health-economic perspective, repeated endovascular sessions for refractory vasospasm can substantially increase resource utilization in comparison with optimized medical therapy, largely through prolonged ICU stays, multiple angiographic procedures, and device-related expenditures. In U.S. practice settings, these downstream costs should be explicitly balanced against the incremental clinical benefit when deciding on escalation beyond first-line medical measures; transparent institutional pathways and multidisciplinary review can help ensure judicious, outcome-oriented use of endovascular resources.¹⁷⁸⁻¹⁸⁰

8. Conclusion

As a serious complication associated with high mortality and morbidity, CV following sSAH warrants special attention in clinical management. The multifactorial pathophysiology of CV involves the interplay of several mechanisms, including oxidative stress due to hemoglobin degradation products, decreased nitric oxide availability, elevated ET-1 levels, inflammation, and endothelial dysfunction. Systematic evaluation of risk factors—based on demographic, clinical, laboratory, and imaging findings—is essential for the success of early diagnosis and preventive

strategies. In the diagnostic process, while DSA remains the gold standard, complementary techniques such as CTA, CT perfusion, MRA, TCD, EEG, SPECT, and cerebral microdialysis enhance diagnostic accuracy and support differential diagnosis and treatment planning. Among pharmacologic therapies, nimodipine remains the only agent supported by high-level evidence. In cases refractory to medical therapy, endovascular interventions—including TBA and intra-arterial vasodilators—serve as potentially life-saving options. However, owing to the associated risks and relatively high costs of these therapies, many aspects should be considered when prescribing them to the patients. In light of current evidence, early diagnosis and optimal management of CV necessitate a multidisciplinary approach, individualized treatment strategies, and future high-quality clinical research to improve outcomes.

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References

- Kaptain GJ, Lanzino G, Kassell NF. Subarachnoid haemorrhage: Epidemiology, risk factors, and treatment options. *Drugs Aging*. 2000;17(3):183-199.
doi: 10.2165/00002512-200017030-00003
- van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: Diagnosis, causes and management. *Brain*. 2001;124(Pt 2):249-278.
doi: 10.1093/brain/124.2.249
- Rincon F, Rossenwasser RH, Dumont A. The epidemiology of admissions of nontraumatic subarachnoid hemorrhage in the United States. *Neurosurgery*. 2013;73(2):217-222.
doi: 10.1227/01.neu.0000430290.93304.33
- Erkan B, Akpinar E, Kiliç Y, *et al.* Results of microsurgical clipping of anterior circulation aneurysms secondary to subarachnoid hemorrhage: 107 cases. *Med J Bakirkoy*. 2023;19(3):328-338.
doi: 10.4274/BMJ.galenos.2023.2023.5-14.
- Lovelock CE, Rinkel GJ, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. *Neurology*. 2010;74(19):1494-1501.
doi: 10.1212/WNL.0b013e3181dd42b3
- Mackey J, Khoury JC, Alwell K, *et al.* Stable incidence but declining case-fatality rates of subarachnoid hemorrhage in a population. *Neurology*. 2016;87(21):2192-2197.
doi: 10.1212/WNL.0000000000003353
- Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. *Stroke*. 1997;28(3):660-664.
doi: 10.1161/01.str.28.3.660
- Hoh BL, Ko NU, Amin-Hanjani S, *et al.* 2023 guideline for the management of patients with aneurysmal subarachnoid hemorrhage: A guideline from the American Heart Association/American Stroke Association. *Stroke*. 2023;54(7):e314-e370. doi:10.1161/STR.0000000000000436. Erratum in: *Stroke*. 2023;54(12):e516.
doi: 10.1161/STR.0000000000000449
- Tjahjadi M, Heinen C, König R, *et al.* Health-related quality of life after spontaneous subarachnoid hemorrhage measured in a recent patient population. *World Neurosurg*. 2013;79(2):296-307.
doi: 10.1016/j.wneu.2012.10.009
- Taufique Z, May T, Meyers E, *et al.* Predictors of poor quality of life 1 year after subarachnoid hemorrhage. *Neurosurgery*. 2016;78(2):256-264.
doi: 10.1227/NEU.0000000000001042
- Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *Stroke*. 2010;41(8):e519-e536.
doi: 10.1161/STROKEAHA.110.581975
- Budohoski KP, Guilfoyle M, Helmy A, *et al.* The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 2014;85(12):1343-1353.
doi: 10.1136/jnnp-2014-307711
- Ecker A, Riemenschneider PA. Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms. *J Neurosurg*. 1951;8:660-667.
doi: 10.3171/jns.1951.8.6.0660
- Allcock JM, Drake CG. Postoperative angiography in cases of ruptured intracranial aneurysm. *J Neurosurg*. 1963;20:752-759.
doi: 10.3171/jns.1963.20.9.0752
- Li K, Barras CD, Chandra RV, *et al.* A review of the management of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2019;126:513-527.
doi: 10.1016/j.wneu.2019.03.083
- Osgood ML. Aneurysmal subarachnoid hemorrhage: Review of the pathophysiology and management strategies. *Curr Neurol Neurosci Rep*. 2021;21(9):50.
doi: 10.1007/s11910-021-01136-9
- Ivanidze J, Sanelli PC. Vasospasm: Role of imaging in detection and monitoring treatment. *Neuroimaging Clin N Am*. 2021;31(2):147-155.
doi: 10.1016/j.nic.2021.01.004
- Bombardieri AM, Seners P, Wouters A, *et al.* Advancing diagnostic precision of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: The potential for a vasospasm index score on perfusion imaging to detect vasospasm. *Eur J Radiol*. 2024;178:111578.
doi: 10.1016/j.ejrad.2024.111578
- Romoli M, Giammello F, Mosconi MG, *et al.* Immunological profile of vasospasm after subarachnoid hemorrhage. *Int J Mol Sci*. 2023;24(10):8856.
doi: 10.3390/ijms24108856
- Medina-Suárez J, Rodríguez-Esparragón F, Sosa-Pérez C, *et al.* A review of genetic polymorphisms and susceptibilities to complications after aneurysmal subarachnoid hemorrhage. *Int J Mol Sci*. 2022;23(23):15427.
doi: 10.3390/ijms232315427

21. Ljevak J, Jerčić KG, Blažeković A, *et al.* Association of eNOS T786C genetic polymorphism with the risk of aneurysmal subarachnoid haemorrhage. *Transl Neurosci.* 2025;16(1):20250368.
doi: 10.1515/tnsci-2025-0368
22. Welty TE, Horner TG. Pathophysiology and treatment of subarachnoid hemorrhage. *Clin Pharm.* 1990;9(1):35-39.
23. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery.* 1980;6(1):1-9.
doi: 10.1227/00006123-198001000-00001
24. Greenberg MS. *Greenberg's Handbook of Neurosurgery.* 10th ed. New York: Thieme; 2023.
25. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg.* 1968;28(1):14-20.
doi: 10.3171/jns.1968.28.1.0014
26. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. *J Neurosurg.* 1988;68(6):985-986.
doi: 10.3171/jns.1988.68.6.0985
27. Frontera JA, Claassen J, Schmidt JM, *et al.* Prediction of symptomatic vasospasm after subarachnoid hemorrhage: The modified Fisher scale. *Neurosurgery.* 2006;59(1):21-27.
doi: 10.1227/01.neu.0000243277.86222.6c
28. Foreman B. The pathophysiology of delayed cerebral ischemia. *J Clin Neurophysiol.* 2016;33(3):174-182.
doi: 10.1097/WNP.0000000000000273
29. Thilak S, Brown P, Whitehouse T, *et al.* Diagnosis and management of subarachnoid haemorrhage. *Nat Commun.* 2024;15(1):1850.
doi: 10.1038/s41467-024-46015-2
30. Suarez JJ, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med.* 2006;354(4):387-396.
doi: 10.1056/NEJMra052732
31. Macdonald RL, Weir BK. Cerebral vasospasm and free radicals. *Free Radic Biol Med.* 1994;16(5):633-643.
doi: 10.1016/0891-5849(94)90064-7
32. Cook DA, Vollrath B. Free radicals and intracellular events associated with cerebrovascular spasm. *Cardiovasc Res.* 1995;30(4):493-500.
33. Won SM, Lee JH, Park UJ, Gwag J, Gwag BJ, Lee YB. Iron mediates endothelial cell damage and blood-brain barrier opening in the hippocampus after transient forebrain ischemia in rats. *Exp Mol Med.* 2011;43(2):121-128.
doi: 10.3858/emmm.2011.43.2.020
34. Pluta RM. Dysfunction of nitric oxide synthases as a cause and therapeutic target in delayed cerebral vasospasm after SAH. *Acta Neurochir Suppl.* 2008;104:139-147.
doi: 10.1007/978-3-211-75718-5_28.
35. Sabri M, Ai J, Knight B, *et al.* Uncoupling of endothelial nitric oxide synthase after experimental subarachnoid hemorrhage. *J Cereb Blood Flow Metab.* 2011;31(1):190-199.
doi: 10.1038/jcbfm.2010.76
36. Friedrich V, Flores R, Muller A, Sehba FA. Escape of intraluminal platelets into brain parenchyma after subarachnoid hemorrhage. *Neuroscience.* 2010;165(3):968-975.
doi: 10.1016/j.neuroscience.2009.10.038
37. Boscolo E, Pavesi G, Zampieri P, *et al.* Endothelial cells from human cerebral aneurysm and arteriovenous malformation release ET-1 in response to vessel rupture. *Int J Mol Med.* 2006;18(5):813-819.
38. Peeyush Kumar T, McBride DW, Dash PK, Matsumura K, Rubi A, Blackburn SL. Endothelial cell dysfunction and injury in subarachnoid hemorrhage. *Mol Neurobiol.* 2019;56(3):1992-2006.
doi: 10.1007/s12035-018-1213-7
39. Sumpio BE, Riley JT, Dardik A. Cells in focus: Endothelial cell. *Int J Biochem Cell Biol.* 2002;34(12):1508-1512.
doi: 10.1016/S1357-2725(02)00075-4
40. Cahill J, Calvert JW, Zhang JH. Mechanisms of early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab.* 2006;26(11):1341-1353.
doi: 10.1038/sj.jcbfm.9600283
41. Alkan T, Tureyen K, Ulutas M, *et al.* Acute and delayed vasoconstriction after subarachnoid hemorrhage: Local cerebral blood flow, histopathology, and morphology in the rat basilar artery. *Arch Physiol Biochem.* 2001;109(2):145-153.
doi: 10.1076/apab.109.2.145.4267
42. Ono S, Date I, Nakajima M, *et al.* Three-dimensional analysis of vasospastic major cerebral arteries in rats with the corrosion cast technique. *Stroke.* 1997;28(8):1631-1637.
doi: 10.1161/01.str.28.8.1631
43. Sehba FA, Friedrich V Jr, Makonnen G, Bederson JB. Acute cerebral vascular injury after subarachnoid hemorrhage and its prevention by administration of a nitric oxide donor. *J Neurosurg.* 2007;106(2):321-329.
doi: 10.3171/jns.2007.106.2.321
44. Koźniewska E, Michalik R, Rafałowska J, *et al.* Mechanisms of vascular dysfunction after subarachnoid hemorrhage. *J Physiol Pharmacol.* 2006;57(Suppl 11):145-160.
45. Dietrich HH, Dacey RG Jr. Molecular keys to the problems of cerebral vasospasm. *Neurosurgery.* 2000;46(3):517-530.
doi: 10.1097/00006123-200003000-00001

46. Ohashi SN, DeLong JH, Kozberg MG, *et al.* Role of inflammatory processes in hemorrhagic stroke. *Stroke*. 2023;54(2):605-619.
doi: 10.1161/STROKEAHA.122.037155
47. Ning W, Lv S, Wang Q, Xu Y. The pivotal role of microglia in injury and the prognosis of subarachnoid hemorrhage. *Neural Regen Res*. 2025;20(7):1829-1848.
doi: 10.4103/NRR.NRR-D-24-00241
48. Lauzier DC, Athiraman U. Role of microglia after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2024;44(6):841-856.
doi: 10.1177/0271678X241237070
49. Wroe WW, Zeineddine HA, Blackburn SL, Aronowski J, McBride DW. The role of neutrophils in vasospasm and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: Is it time for a SAH clinical trial targeting neutrophils? *J Cereb Blood Flow Metab*. 2025;271678X251370858.
doi: 10.1177/0271678X251370858
50. Mehra A, Gomez F, Bischof H, Diedrich D, Laudanski K. Cortical spreading depolarization and delayed cerebral ischemia; rethinking secondary neurological injury in subarachnoid hemorrhage. *Int J Mol Sci*. 2023;24(12):9883.
doi: 10.3390/ijms24129883
51. Horst V, Kola V, Lemale CL, *et al.* Spreading depolarization and angiographic spasm are separate mediators of delayed infarcts. *Brain Commun*. 2023;5(2):fcad080.
doi: 10.1093/braincomms/fcad080
52. Guo ZN, Shao A, Tong LS, Sun W, Liu J, Yang Y. The role of nitric oxide and sympathetic control in cerebral autoregulation in the setting of subarachnoid hemorrhage and traumatic brain injury. *Mol Neurobiol*. 2016;53(6):3606-3615.
doi: 10.1007/s12035-015-9308-x
53. Hamner JW, Tan CO, Lee K, Cohen MA, Taylor JA. Sympathetic control of the cerebral vasculature in humans. *Stroke*. 2010;41(1):102-109.
doi: 10.1161/STROKEAHA.109.557132
54. Faraci FM. Reactive oxygen species: Influence on cerebral vascular tone. *J Appl Physiol (1985)*. 2006;100(2):739-743.
doi: 10.1152/japplphysiol.01044.2005
55. Galley HF, Webster NR. Physiology of the endothelium. *Br J Anaesth*. 2004;93(1):105-113.
doi: 10.1093/bja/ae163
56. Lai PMR, Gormley WB, Patel N, Frerichs KU, Aziz-Sultan MA, Du R. Age-dependent radiographic vasospasm and delayed cerebral ischemia in women after aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2019;130:e230-e235.
doi: 10.1016/j.wneu.2019.06.040
57. Rumalla K, Lin M, Ding L, *et al.* Risk factors for cerebral vasospasm in aneurysmal subarachnoid hemorrhage: A population-based study of 8346 patients. *World Neurosurg*. 2021;145:e233-e241.
doi: 10.1016/j.wneu.2020.10.008
58. Zhao L, Cheng C, Peng L, *et al.* Alcohol abuse associated with increased risk of angiographic vasospasm and delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage requiring mechanical ventilation. *Front Cardiovasc Med*. 2022;9:825890.
doi: 10.3389/fcvm.2022.825890
59. Mijiti M, Mijiti P, Axier A, *et al.* Incidence and predictors of angiographic vasospasm, symptomatic vasospasm and cerebral infarction in Chinese patients with aneurysmal subarachnoid hemorrhage. *PLoS One*. 2016;11(12):e0168657.
doi: 10.1371/journal.pone.0168657
60. Zhang J, Lo YL, Li MC, *et al.* Risk of re-rupture, vasospasm, or re-stroke after clipping or coiling of ruptured intracranial aneurysms: Long-term follow-up with a propensity score-matched, population-based cohort study. *J Pers Med*. 2021;11(11):1209.
doi: 10.3390/jpm11111209
61. Buce-Satoba I, Rozkalne D, Mamaja B, Krumina G, Ozolina A. Leukocytosis and C-reactive protein may predict development of secondary cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. *Medicina (Kaunas)*. 2022;58(2):323.
doi: 10.3390/medicina58020323
62. Ho Kim J, Jun Yi H, Kim BT, Shin DS. Clinical relevance of serum procalcitonin in patients with aneurysmal subarachnoid hemorrhage. *Exp Ther Med*. 2022;24(5):653.
doi: 10.3892/etm.2022.11590
63. Abdelnaseer MM, Nemr AA, Ahmed SM, *et al.* Role of serum biomarkers and transcranial Doppler in predicting cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Egypt J Neurol Psychiatry Neurosurg*. 2020;56:27.
doi: 10.1186/s41983-020-0156-x
64. Goertz L, Kabbasch C, Styczen H, *et al.* Impact of aneurysm morphology on aneurysmal subarachnoid hemorrhage severity, cerebral infarction and functional outcome. *J Clin Neurosci*. 2021;89:343-348.
doi: 10.1016/j.jocn.2021.04.029
65. Colip CG, Wo S, Hippe DS, *et al.* Computed tomography angiography findings predictive of post-intervention vasospasm in patients with aneurysmal subarachnoid hemorrhage. *Br J Radiol*. 2021;94(1121):20200893.
doi: 10.1259/bjr.20200893

66. Darkwah Oppong M, Iannaccone A, Gembruch O, *et al.* Vasospasm-related complications after subarachnoid hemorrhage: The role of patients' age and sex. *Acta Neurochir (Wien)*. 2018;160(7):1393-1400.
doi: 10.1007/s00701-018-3549-1
67. Pasqualin A. Epidemiology and pathophysiology of cerebral vasospasm following subarachnoid hemorrhage. *J Neurosurg Sci*. 1998;42(1 Suppl 1):15-21.
68. Kassell NF, Sasaki T, Colohan AR, Nazar G. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke*. 1985;16(4):562-572.
doi: 10.1161/01.str.16.4.562
69. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2(7872):81-84.
doi: 10.1016/S0140-6736(74)91639-0
70. Drake CG, Hunt WE, Kassell N, *et al.* Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. *J Neurosurg*. 1988;68:985-986.
doi: 10.3171/jns.1988.68.6.0985
71. Müller D, Müller O. Neurointensivmedizin: Aneurysmatische Subarachnoidalblutung—State of the Art [Neurointensive care: Aneurysmal subarachnoid hemorrhage-state of the art]. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 2018;53(10):654-667.
72. Marshall SA, Nyquist P, Ziai WC. The role of transcranial Doppler ultrasonography in the diagnosis and management of vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurg Clin N Am*. 2010;21:291-303.
doi: 10.1016/j.nec.2009.10.010
73. Leffers AM, Wagner A. Neurologic complications of cerebral angiography: A retrospective study of complication rate and patient risk factors. *Acta Radiol*. 2000;41(3):204-210.
doi: 10.1080/028418500127345299.
74. Willinsky RA, Taylor SM, Terbrugge K, Farb RI, Tomlinson G, Montanera W. Neurologic complications of cerebral angiography: Prospective analysis of 2,899 procedures and review of the literature. *Radiology*. 2003;227(2):522-528.
doi: 10.1148/radiol.2272012071
75. Shankar JJ, Tan IY, Krings T, Terbrugge K, Agid R. CT angiography for evaluation of cerebral vasospasm following acute subarachnoid haemorrhage. *Neuroradiology*. 2012;54(3):197-203.
doi: 10.1007/s00234-011-0876-9
76. Sanelli PC, Ougorets I, Johnson CE, Riina HA, Biondi A. Using CT in the diagnosis and management of patients with cerebral vasospasm. *Semin Ultrasound CT MR*. 2006;27(3):194-206.
doi: 10.1053/j.sult.2006.02.004
77. Dankbaar JW, Rijsdijk M, van der Schaaf IC, *et al.* Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Neuroradiology*. 2009;51(12):813-819.
doi: 10.1007/s00234-009-0575-y
78. Aaslid R. Transcranial Doppler assessment of cerebral vasospasm. *Eur J Ultrasound*. 2002;16(1-2):3-10.
doi: 10.1016/S0929-8266(02)00045-9
79. Bell TE, LaGrange KM, Maier CM, Steinberg GK. Transcranial Doppler: Correlation of blood velocity measurement with clinical status in subarachnoid hemorrhage. *J Neurosci Nurs*. 1992;24(4):215-219.
doi: 10.1097/01376517-199208000-00008
80. Sloan MA, Haley EC Jr, Kassell NF, *et al.* Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. *Neurology*. 1989;39(11):1514-1518.
doi: 10.1212/WNL.39.11.1514
81. Sloan MA, Burch CM, Wozniak MA, *et al.* Transcranial Doppler detection of vertebrobasilar vasospasm following subarachnoid hemorrhage. *Stroke*. 1994;25(11):2187-2197.
doi: 10.1161/01.str.25.11.2187
82. Bacigaluppi S, Zona G, Secci F, *et al.* Diagnosis of cerebral vasospasm and risk of delayed cerebral ischemia related to aneurysmal subarachnoid haemorrhage: An overview of available tools. *Neurosurg Rev*. 2015;38(4):603-618.
doi: 10.1007/s10143-015-0617-3
83. Dreier JP, Sakowitz OW, Harder A, *et al.* Focal laminar cortical MR signal abnormalities after subarachnoid hemorrhage. *Ann Neurol*. 2002;52:825-829.
doi: 10.1002/ana.10383
84. Weidauer S, Vatter H, Beck J, *et al.* Focal laminar cortical infarcts following aneurysmal subarachnoid haemorrhage. *Neuroradiology*. 2008;50:1-8.
doi: 10.1007/s00234-007-0294-1
85. van der Kleij LA, De Vis JB, Olivot JM, *et al.* Magnetic resonance imaging and cerebral ischemia after aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Stroke*. 2017;48(1):239-245.
doi: 10.1161/STROKEAHA.116.011707
86. Claassen J, Hirsch LJ, Kreiter KT, *et al.* Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. *Clin Neurophysiol*. 2004;115(12):2699-2710.
doi: 10.1016/j.clinph.2004.06.017
87. Claassen J, Mayer SA, Hirsch LJ. Continuous EEG monitoring in patients with subarachnoid hemorrhage.

- J Clin Neurophysiol.* 2005;22(2):92-98.
doi: 10.1097/01.wnp.0000145006.02048.3a
88. Latchaw RE, Yonas H, Hunter GJ, *et al.* Guidelines and recommendations for perfusion imaging in cerebral ischemia: A scientific statement for healthcare professionals by the writing group on perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. *Stroke.* 2003;34(4):1084-1104.
doi: 10.1161/01.STR.0000064840.99271.9E
 89. Johnson DW, Stringer WA, Marks MP, Yonas H, Good WF, Gur D. Stable xenon CT cerebral blood flow imaging: Rationale for and role in clinical decision making. *AJNR Am J Neuroradiol.* 1991;12(2):201-213.
 90. Schubert GA, Weinmann C, Seiz M, *et al.* Cerebrovascular insufficiency as the criterion for revascularization procedures in selected patients: A correlation study of xenon contrast-enhanced CT and PWI. *Neurosurg Rev.* 2009;32(1):29-35; discussion 35-36.
doi: 10.1007/s10143-008-0159-z
 91. Reinprecht A, Czech T, Asenbaum S, Podreka I, Schmidbauer M. Low cerebrovascular reserve capacity in long-term follow-up after subarachnoid hemorrhage. *Surg Neurol.* 2005;64(2):116-120; discussion 121.
doi: 10.1016/j.surneu.2004.12.017
 92. Bacigaluppi S, Dehdashti AR, Agid R, Krings T, Tymianski M, Mikulis DJ. The contribution of imaging in diagnosis, preoperative assessment, and follow-up of moyamoya disease: A review. *Neurosurg Focus.* 2009;26(4):E3.
doi: 10.3171/2009.01.FOCUS08296
 93. Wintermark M, Sesay M, Barbier E, *et al.* Comparative overview of brain perfusion imaging techniques. *Stroke.* 2005;36(9):e83-e99.
doi: 10.1161/01.STR.0000177884.72657.8b
 94. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science.* 1977;198(4323):1264-1267.
doi: 10.1126/science.929199
 95. Reynolds EO, Wyatt JS, Azzopardi D, *et al.* New non-invasive methods for assessing brain oxygenation and haemodynamics. *Br Med Bull.* 1988;44(4):1052-1075.
doi: 10.1093/oxfordjournals.bmb.a072289
 96. Sakatani K, Yokose N, Katagiri A, *et al.* Progress in NIRS monitoring of cerebral blood flow. *Brain Nerve.* 2011;63(9):955-961. Japanese.
 97. Goodman JC, Robertson CS. Microdialysis: Is it ready for prime time? *Curr Opin Crit Care.* 2009;15(2):110-117.
doi: 10.1097/MCC.0b013e328325d142
 98. Unterberg AW, Sakowitz OW, Sarrafzadeh AS, Benndorf G, Lanksch WR. Role of bedside microdialysis in the diagnosis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 2001;94(5):740-749.
doi: 10.3171/jns.2001.94.5.0740
 99. Sheinberg M, Kanter MJ, Robertson CS, Contant CE, Narayan RK, Grossman RG. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *J Neurosurg.* 1992;76(2):212-217.
doi: 10.3171/jns.1992.76.2.0212
 100. Nakamura T, Tatara N, Morisaki K, Kawakita K, Nagao S. Cerebral oxygen metabolism monitoring under hypothermia for severe subarachnoid hemorrhage: Report of eight cases. *Acta Neurol Scand.* 2002;106(5):314-318.
doi: 10.1034/j.1600-0404.2002.01300.x
 101. Schneider GH, von Helden A, Lanksch WR, Unterberg A. Continuous monitoring of jugular bulb oxygen saturation in comatose patients: Therapeutic implications. *Acta Neurochir (Wien).* 1995;134(1-2):71-75.
doi: 10.1007/BF01428507
 102. Etminan N, Macdonald RL. Management of aneurysmal subarachnoid hemorrhage. *Handb Clin Neurol.* 2017;140:195-228.
doi: 10.1016/B978-0-444-63600-3.00012-X
 103. Greenberg ED, Gold R, Reichman M, *et al.* Diagnostic accuracy of CT angiography and CT perfusion for cerebral vasospasm: A meta-analysis. *AJNR Am J Neuroradiol.* 2010;31(10):1853-1860.
doi: 10.3174/ajnr.A2246
 104. Tamatani S, Sasaki O, Takeuchi S, Fujii Y, Koike T, Tanaka R. Detection of delayed cerebral vasospasm after rupture of intracranial aneurysms by magnetic resonance angiography. *Neurosurgery.* 1997;40(4):748-753.
doi: 10.1097/00006123-199704000-00017
 105. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. *Radiology.* 2000;217:331-345.
doi: 10.1148/radiology.217.2.r00nv24331
 106. Powsner RA, O'Tuama LA, Jabre A, Melhem ER. SPECT imaging in cerebral vasospasm following subarachnoid hemorrhage. *J Nucl Med.* 1998;39(5):765-769.
 107. Treggiari MM, Walder B, Suter PM, Romand JA. Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage. *J Neurosurg.* 2003;98(5):978-984.
doi: 10.3171/jns.2003.98.5.0978
 108. Loan JJM, Wiggins AN, Brennan PM. Medically induced hypertension, hypervolaemia and haemodilution for the treatment and prophylaxis of vasospasm following

- aneurysmal subarachnoid haemorrhage: Systematic review. *Br J Neurosurg*. 2018;32(2):157-164.
doi: 10.1080/02688697.2018.1426720
109. Egge A, Waterloo K, Sjøholm H, Solberg T, Ingebrigtsen T, Romner B. Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: A clinical, prospective, randomized, controlled study. *Neurosurgery*. 2001;49(3):593-605.
doi: 10.1097/00006123-200109000-00012
 110. Lennihan L, Mayer SA, Fink ME, *et al*. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial. *Stroke*. 2000;31(2):383-391.
doi: 10.1161/01.STR.31.2.383
 111. Deshaies EM, Boulos AS, Popp AJ. Perioperative medical management of cerebral vasospasm. *Neurol Res*. 2009;31(6):644-650.
doi: 10.1179/174313209X382340
 112. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G, European Stroke Organization. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35(2):93-112.
doi: 10.1159/000346087
 113. Kiser TH. Pharmacologic options for prevention and management of cerebral vasospasm in aneurysmal subarachnoid hemorrhage. *Hosp Pharm*. 2013;48(5 Suppl):S2-S9.
doi: 10.1310/hpj48S5-S2.
 114. Odom MJ, Zuckerman SL, Mocco J. The role of magnesium in the management of cerebral vasospasm. *Neurol Res Int*. 2013;2013:943914.
doi: 10.1155/2013/943914
 115. Wong GK, Poon WS, Chan MT, *et al*. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): A randomized, double-blinded, placebo-controlled, multicenter phase III trial. *Stroke*. 2010;41(5):921-926.
doi: 10.1161/STROKEAHA.109.571125
 116. Dorhout Mees SM, Algra A, Vandertop WP, *et al*. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): A randomised placebo-controlled trial. *Lancet*. 2012;380(9836):44-49.
doi: 10.1016/S0140-6736(12)60724-7
 117. Liu J, Chen Q. Effect of statins treatment for patients with aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis of observational studies and randomized controlled trials. *Int J Clin Exp Med*. 2015;8(5):7198-7208.
 118. Su SH, Xu W, Hai J, Wu YF, Yu F. Effects of statins use for patients with aneurysmal subarachnoid hemorrhage: A meta-analysis of randomized controlled trials. *Sci Rep*. 2014;4:4573.
doi: 10.1038/srep04573
 119. Shen J, Huang KY, Zhu Y, *et al*. Effect of statin treatment on vasospasm-related morbidity and functional outcome in patients with aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *J Neurosurg*. 2017;127(2):291-301.
doi: 10.3171/2016.5.JNS152900
 120. Akhigbe T, Zolnourian A, Bulters D. Cholesterol-reducing agents for treatment of aneurysmal subarachnoid hemorrhage: Systematic review and meta-analysis of randomized controlled trials. *World Neurosurg*. 2017;101:476-485.
doi: 10.1016/j.wneu.2017.01.125
 121. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD, STASH Collaborators. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): A multicentre randomised phase 3 trial. *Lancet Neurol*. 2014;13(7):666-675.
doi: 10.1016/S1474-4422(14)70084-5
 122. Macdonald RL, Kassell NF, Mayer S, *et al*. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): Randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke*. 2008;39(11):3015-3021.
doi: 10.1161/STROKEAHA.108.519942
 123. Macdonald RL, Higashida RT, Keller E, *et al*. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: A randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol*. 2011;10(7):618-625.
doi: 10.1016/S1474-4422(11)70108-9
 124. Macdonald RL, Higashida RT, Keller E, *et al*. Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling. *Stroke*. 2012;43(6):1463-1469.
doi: 10.1161/STROKEAHA.111.648980
 125. Endo H, Hagihara Y, Kimura N, *et al*. Effects of clazosentan on cerebral vasospasm-related morbidity and all-cause mortality after aneurysmal subarachnoid hemorrhage: Two randomized phase 3 trials in Japanese patients. *J Neurosurg*. 2022;137(6):1707-1717.
doi: 10.3171/2022.2.JNS212914
 126. Mistry AM, Mistry EA, Ganesh Kumar N, Froehler MT, Fusco MR, Chitale RV. Corticosteroids in the management of hyponatremia, hypovolemia, and vasospasm in subarachnoid hemorrhage: A meta-analysis. *Cerebrovasc*

- Dis.* 2016;42(3-4):263-271.
doi: 10.1159/000446251
127. Daou BJ, Koduri S, Thompson BG, Chaudhary N, Pandey AS. Clinical and experimental aspects of aneurysmal subarachnoid hemorrhage. *CNS Neurosci Ther.* 2019;25(10):1096-1112.
doi: 10.1111/cns.13222
128. Abulhasan YB, Ortiz Jimenez J, Teitelbaum J, Simoneau G, Angle MR. Milrinone for refractory cerebral vasospasm with delayed cerebral ischemia. *J Neurosurg.* 2020;134(3):971-982.
doi: 10.3171/2020.1.JNS193107
129. Lakhal K, Hivert A, Alexandre PL, *et al.* Intravenous milrinone for cerebral vasospasm in subarachnoid hemorrhage: The MILRISPASM controlled before-after study. *Neurocrit Care.* 2021;35(3):669-679.
doi: 10.1007/s12028-021-01331-z
130. Bernier TD, Schontz MJ, Izzy S, *et al.* Treatment of subarachnoid hemorrhage-associated delayed cerebral ischemia with milrinone: A review and proposal. *J Neurosurg Anesthesiol.* 2021;33(3):195-202.
doi: 10.1097/ANA.0000000000000755
131. Qureshi AI, Ishfaq A, Ishfaq MF, *et al.* Therapeutic benefit of cilostazol in patients with aneurysmal subarachnoid hemorrhage: A meta-analysis of randomized and nonrandomized studies. *J Vasc Interv Neurol.* 2018;10(2):33-40.
132. Senbokuya N, Kinouchi H, Kanemaru K, *et al.* Effects of cilostazol on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: A multicenter prospective, randomized, open-label blinded end point trial. *J Neurosurg.* 2013;118(1):121-130.
doi: 10.3171/2012.9.JNS12492
133. Saber H, Desai A, Palla M, Mohamed W, Seraji-Bozorgzad N, Ibrahim M. Efficacy of cilostazol in prevention of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: A meta-analysis. *J Stroke Cerebrovasc Dis.* 2018;27(11):2979-2985.
doi: 10.1016/j.jstrokecerebrovasdis.2018.06.027
134. Zhao J, Zhou D, Guo J, *et al.* Efficacy and safety of fasudil in patients with subarachnoid hemorrhage: Final results of a randomized trial of fasudil versus nimodipine. *Neurol Med Chir (Tokyo).* 2011;51(10):679-683.
doi: 10.2176/nmc.51.679
135. Saito A, Inoue M, Kon H, *et al.* Effectiveness of intraarterial administration of fasudil hydrochloride for preventing symptomatic vasospasm after subarachnoid hemorrhage. *Acta Neurochir Suppl.* 2015;120:297-301.
doi: 10.1007/978-3-319-04981-6_50
136. Liu GJ, Wang ZJ, Wang YF, *et al.* Systematic assessment and meta-analysis of the efficacy and safety of fasudil in the treatment of cerebral vasospasm in patients with subarachnoid hemorrhage. *Eur J Clin Pharmacol.* 2012;68(2):131-139.
doi: 10.1007/s00228-011-1100-x
137. Dhar R, Washington C, Diringier M, *et al.* Acute effect of intravenous sildenafil on cerebral blood flow in patients with vasospasm after subarachnoid hemorrhage. *Neurocrit Care.* 2016;25(2):201-204.
doi: 10.1007/s12028-016-0243-0
138. Atalay B, Caner H, Cekinmez M, Ozen O, Celasun B, Altinors N. Systemic administration of phosphodiesterase V inhibitor, sildenafil citrate, for attenuation of cerebral vasospasm after experimental subarachnoid hemorrhage. *Neurosurgery.* 2006;59(5):1102-1107.
doi: 10.1227/01.NEU.0000245605.22817.44
139. Lilla N, Hartmann J, Koehler S, Ernestus RI, Westermaier T. Early NO-donor treatment improves acute perfusion deficit and brain damage after experimental subarachnoid hemorrhage in rats. *J Neurol Sci.* 2016;370:312-319.
doi: 10.1016/j.jns.2016.09.032
140. Yilmaz C, Cansever T, Kircelli A, *et al.* The effects of proanthocyanidin on vasospasm after experimental subarachnoidal hemorrhage in rats. *Turk Neurosurg.* 2018;28(4):667-674.
doi: 10.5137/1019-5149.JTN.14781-15.3
141. Aladag MA, Turkoz Y, Parlakpinar H, Gul M. Nebivolol attenuates cerebral vasospasm both by increasing endothelial nitric oxide and by decreasing oxidative stress in an experimental subarachnoid haemorrhage. *Br J Neurosurg.* 2017;31(4):439-445.
doi: 10.1080/02688697.2017.1297367
142. Siuta M, Zuckerman SL, Mocco J. Nitric oxide in cerebral vasospasm: theories, measurement, and treatment. *Neurol Res Int.* 2013;2013:972417.
doi: 10.1155/2013/972417
143. Veldeman M, Höllig A, Clusmann H, Stevanovic A, Rossaint R, Coburn M. Delayed cerebral ischaemia prevention and treatment after aneurysmal subarachnoid haemorrhage: A systematic review. *Br J Anaesth.* 2016;117(1):17-40.
doi: 10.1093/bja/aew095
144. Siasios I, Kapsalaki EZ, Fountas KN. Cerebral vasospasm pharmacological treatment: An update. *Neurol Res Int.* 2013;2013:571328.
doi: 10.1155/2013/571328
145. Liu YF, Qiu HC, Su J, *et al.* Drug treatment of cerebral vasospasm after subarachnoid hemorrhage following aneurysms. *Chin Neurosurg J.* 2016;2:4.

146. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: Looking beyond vasospasm. *Br J Anaesth*. 2012;109(3):315-329.
doi: 10.1093/bja/aes264
147. Dorhout Mees SM, van den Bergh WM, Algra A, Rinkel GJ. Antiplatelet therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;2007(4):CD006184.
doi: 10.1002/14651858.CD006184.pub2
148. Li L, Zhou F, Zhao X, *et al*. The role of lumbar drainage in symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Chin J Emerg Med*. 2015;24:1357-1363.
149. Panni P, Fugate JE, Rabinstein AA, Lanzino G. Lumbar drainage and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: A systematic review. *J Neurosurg Sci*. 2017;61(6):665-672.
doi: 10.23736/S0390-5616.16.03151-9
150. Ota N, Matsukawa H, Kamiyama H, *et al*. Preventing cerebral vasospasm after aneurysmal subarachnoid hemorrhage with aggressive cisternal clot removal and nicardipine. *World Neurosurg*. 2017;107:630-640.
doi: 10.1016/j.wneu.2017.08.088
151. Koyanagi M, Fukuda H, Lo B, *et al*. Effect of intrathecal milrinone injection via lumbar catheter on delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2018;128(3):717-722.
doi: 10.3171/2016.10.JNS162227
152. Sadamasa N, Yoshida K, Narumi O, Chin M, Yamagata S. Milrinone via lumbar subarachnoid catheter for vasospasm after aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2014;21(3):470-475.
doi: 10.1007/s12028-014-9996-5
153. Ader J. Guidelines in action: volume and blood pressure management after aneurysmal subarachnoid hemorrhage. *Stroke*. 2024;55(2):e39-e41.
doi: 10.1161/STROKEAHA.123.044957
154. Maeda T, Okawara M, Osakabe M, Yamaguchi H, Maeda T, Kurita H. Initial real-world experience of clazosentan for subarachnoid hemorrhage in Japan. *World Neurosurg X*. 2023;21:100253.
doi: 10.1016/j.wnsx.2023.100253
155. Pontes JPM, Santos MDC, Gibram FC, *et al*. Efficacy and safety of clazosentan after aneurysmal subarachnoid hemorrhage: An updated meta-analysis. *Neurosurgery*. 2023;93(6):1208-1219.
doi: 10.1227/neu.0000000000002601
156. Lannes M, Teitelbaum J, del Pilar Cortés M, Cardoso M, Angle M. Milrinone and homeostasis to treat cerebral vasospasm associated with subarachnoid hemorrhage: The Montreal Neurological Hospital protocol. *Neurocrit Care*. 2012;16(3):354-362.
doi: 10.1007/s12028-012-9701-5
157. Huang RQ, Jiang FG, Feng ZM, Wang TY. Nicardipine in the treatment of aneurysmal subarachnoid haemorrhage: A meta-analysis of published data. *Acta Neurol Belg*. 2013;113(1):3-6.
doi: 10.1007/s13760-012-0142-x
158. Sadan O, Waddel H, Moore R, *et al*. Does intrathecal nicardipine for cerebral vasospasm following subarachnoid hemorrhage correlate with reduced delayed cerebral ischemia? A retrospective propensity score-based analysis. *J Neurosurg*. 2021;136(1):115-124.
doi: 10.3171/2020.12.JNS203673
159. Dorhout Mees SM, Rinkel GJ, Feigin VL, *et al*. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;2007(3):CD000277.
doi: 10.1002/14651858.CD000277.pub3
160. Barth M, Capelle HH, Weidauer S, *et al*. Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: A prospective, randomized, double-blind phase IIa study. *Stroke*. 2007;38(2):330-336.
doi: 10.1161/01.STR.0000254601.74596.0f
161. Lee KS, Chari A, Motiwala M, Khan NR, Arthur AS, Lawton MT. Effectiveness of cerebrospinal fluid lumbar drainage among patients with aneurysmal subarachnoid hemorrhage: An updated systematic review and meta-analysis. *World Neurosurg*. 2024;183:246-253.e12.
doi: 10.1016/j.wneu.2024.01.062
162. Liang C, Yang L, Guo S. Serial lumbar puncture reduces cerebrospinal fluid infection during removal of hemorrhagic CSF in aneurysmal subarachnoid hemorrhage after endovascular coiling. *J Biomed Res*. 2018;32(4):305-310.
doi: 10.7555/JBR.32.20170028
163. Pierot L, Aggour M, Moret J. Vasospasm after aneurysmal subarachnoid hemorrhage: Recent advances in endovascular management. *Curr Opin Crit Care*. 2010;16(2):110-116.
doi: 10.1097/MCC.0b013e3283372ef2
164. Miley JT, Tariq N, Souslian FG, *et al*. Comparison between angioplasty using compliant and noncompliant balloons for treatment of cerebral vasospasm associated with subarachnoid hemorrhage. *Neurosurgery*. 2011;69(2 Suppl Operative):ons161-ons168.
doi: 10.1227/NEU.0b013e31822a8976
165. Zwienenberg-Lee M, Hartman J, Rudisill N, *et al*. Effect of

- prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: Results of a phase II multicenter, randomized, clinical trial. *Stroke*. 2008;39(6):1759-1765.
doi: 10.1161/STROKEAHA.107.502666
166. Duman E, Karakoç F, Pinar HU, Dogan R, Firat A, Yıldırım E. Higher dose intra-arterial milrinone and intra-arterial combined milrinone-nimodipine infusion as a rescue therapy for refractory cerebral vasospasm. *Interv Neuroradiol*. 2017;23(6):636-643.
doi: 10.1177/1591019917732288
 167. McGuinness B, Gandhi D. Endovascular management of cerebral vasospasm. *Neurosurg Clin N Am*. 2010;21(2):281-290.
doi: 10.1016/j.nec.2009.10.007
 168. Stiefel ME, Spiotta AM, Udoetuk JD, *et al*. Intra-arterial papaverine used to treat cerebral vasospasm reduces brain oxygen. *Neurocrit Care*. 2006;4(2):113-118.
doi: 10.1385/NCC.4:2:113
 169. López-Rueda A, Vargas A, Piñana C, *et al*. Angioplasty with a stent retriever to treat vasospasm secondary to subarachnoid hemorrhage due to an aneurysm: A multicenter study of safety and efficacy. *Radiologia (Engl Ed)*. 2022;64(2):103-109.
doi: 10.1016/j.rxeng.2020.04.009
 170. Bhogal P, Loh Y, Brouwer P, Andersson T, Söderman M. Treatment of cerebral vasospasm with self-expandable retrievable stents: Proof of concept. *J Neurointerv Surg*. 2017;9(1):52-59.
doi: 10.1136/neurintsurg-2016-012546
 171. Hensler J, Wodarg F, Madjidyar J, *et al*. Efficacy and safety in the use of stent-retrievers for treatment of cerebral vasospasms after subarachnoid hemorrhage. *Interv Neuroradiol*. 2023;29(3):277-284.
doi: 10.1177/15910199221086389
 172. Yoshimoto T, Hosoki S, Tanaka K, *et al*. Parallel stent retriever mechanical thrombectomy of an acute internal carotid artery occlusion refractory to standard techniques: A case report. *Front Stroke*. 2023;2:1066491.
doi: 10.3389/fstro.2023.1066491
 173. Khanafer A, von Gottberg P, Albiña-Palmarola P, *et al*. Is stent retraction to relieve arterial cerebral vasospasm caused by SAH (Stent-ReLACSS) using PRELAX the long-awaited solution for treatment of posthemorrhagic cerebral vasospasm? Treatment of posthemorrhagic cerebral vasospasm with PRESET and PRELAX: technical aspects, efficacy, and safety margins in a case series. *Clin Neuroradiol*. 2024;34(3):649-662.
doi: 10.1007/s00062-024-01402-6
 174. Pandey AS, Elias AE, Chaudhary N, Thompson BG, Gemmete JJ. Endovascular treatment of cerebral vasospasm: Vasodilators and angioplasty. *Neuroimaging Clin N Am*. 2013;23(4):593-604.
doi: 10.1016/j.nic.2013.03.008
 175. Sokolowski JD, Chen CJ, Ding D, *et al*. Endovascular treatment for cerebral vasospasm following aneurysmal subarachnoid hemorrhage: Predictors of outcome and retreatment. *J Neurointerv Surg*. 2018;10(4):367-374.
doi: 10.1136/neurintsurg-2017-013363
 176. Ditz C, Neumann A, Wojak J, *et al*. Repeated endovascular treatments in patients with recurrent cerebral vasospasms after subarachnoid hemorrhage: A worthwhile strategy? *World Neurosurg*. 2018;112:e791-e798.
doi: 10.1016/j.wneu.2018.01.156
 177. Boulouis G, Labeyrie MA, Raymond J, *et al*. Treatment of cerebral vasospasm following aneurysmal subarachnoid haemorrhage: A systematic review and meta-analysis. *Eur Radiol*. 2017;27(8):3333-3342.
doi: 10.1007/s00330-016-4702-y
 178. Koester SW, Catapano JS, Rumalla K, *et al*. Health care expenditures associated with delayed cerebral ischemia following subarachnoid hemorrhage: A propensity-adjusted analysis. *World Neurosurg*. 2022;167:e600-e606.
doi: 10.1016/j.wneu.2022.08.057
 179. Thompson JC, Chalet FX, Manalastas EJ, Hawkins N, Sarri G, Talbot DA. Economic and humanistic burden of cerebral vasospasm and its related complications after aneurysmal subarachnoid hemorrhage: A systematic literature review. *Neurol Ther*. 2022;11(2):597-620.
doi: 10.1007/s40120-022-00348-6
 180. Ma YH, Shang R, Li SH, Wang T, Lin S, Zhang CW. Efficacy of endovascular therapy for cerebral vasospasm following aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Front Neurol*. 2024;15:1360511.
doi: 10.3389/fneur.2024.1360511