# Invasive interventional management of post-hemorrhagic cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage

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## ABSTRACT

Current clinical practice standards are addressed for the invasive interventional management of post-hemorrhagic cerebral vasospasm (PHCV) in patients with aneurysmal subarachnoid hemorrhage. The conclusions, based on an assessment by the Standards Committee of the Society of Neurointerventional Surgery, included a critical review of the literature using guidelines for evidence based medicine proposed by the Stroke Council of the American Heart Association and the University of Oxford, Centre for Evidence Based Medicine. Specifically examined were the safety and efficacy of established invasive interventional therapies, including transluminal balloon angioplasty (TBA) and intra-arterial vasodilator infusion therapy (IAVT). The assessment shows that these invasive interventional therapies may be beneficial and may be considered for PHCV—that is, symptomatic with cerebral ischemia and refractory to maximal medical management. As outlined in this document, IAVT may be beneficial for the management of PHCV involving the proximal and/or distal intradural cerebral circulation. TBA may be beneficial for the management of PHCV that involves the proximal intradural cerebral circulation. The assessment shows that for the indications described above, TBA and IAVT are classified as Class IIb, Level B interventions according to the American Heart Association guidelines, and Level 4, Grade C interventions according to the University of Oxford Centre for Evidence Based Medicine guidelines.

## INTRODUCTORY REMARKS

Post-hemorrhagic cerebral vasospasm (PHCV), a well known complication of aneurysmal subarachnoid hemorrhage (SAH), is responsible for significant morbidity and mortality among SAH patients.[1 2] Morbidity and mortality are related to the development of cerebral ischemia and infarction in affected vascular territories.[3] Recent studies have suggested that other undefined factors also contribute to the resulting neurological damage.[4] Nevertheless, angiographically demonstrable vasoconstriction is the most important modifiable risk factor for neurological deterioration and poor outcome.

The precise events that lead to cerebral arterial narrowing in PHCV remain unknown. Numerous inciting factors have been implicated, including erythrocyte degradation products, serum derived lipids and hematogenic proteins. Presumably, the inciting factors trigger a cascade of biochemical and immunoinflammatory reactions that ultimately lead to unopposed activation of the contractile apparatus within cerebrovascular smooth muscle cells. Although loss of luminal caliber is initially reversible, if the process is sustained, vessel wall fibrosis can lead to irreversible stenosis.[5]

There is wide variability in the frequency, intensity and clinical significance of PHCV after aneurysmal SAH. The likelihood of developing PHCV and its severity most strongly correlates with the amount of blood entering the subarachnoid space.[6 7]

Although large focal subarachnoid hematomas will affect adjacent pial arteries most severely, PHCV is often multifocal and may involve remote vascular territories. PHCV has a predictably delayed onset after cerebral aneurysm rupture. It generally does not begin until 3–5 days after the ictus but earlier onset is observed. The PHCV process is characteristically monophasic with an initial period of worsening vasoconstriction, peaking in approximately 10–14 days followed by a gradual return to normal arterial caliber by 2–4 weeks. Delayed cerebral ischemia (DCI) secondary to PHCV may result in severe permanent disability or death. DCI may be partially or completely reversible when effective treatment is administered. Although reversible constriction of the cerebral arteries can be shown angiographically in up to 70% of patients with aneurysmal SAH, DCI only develops in 20–30% of cases.[8–10] DCI and infarction strongly correlate with the angiographic severity of vasospasm and nearly half of patients who experience severe vasospasm will develop territory specific cerebral infarctions.[3]

## LITERATURE REVIEW

The National Library of Medicine database (PubMed 1966–2011) was searched electronically: (1) to identify relevant peer reviewed publications containing outcome data for the procedures under examination to be used as benchmarks for quality assessment; (2) to assess the collective experience with a view to identifying potential risk adjustment variables; and (3) to identify data that can be used to develop monitoring protocols to track the efficacy and appropriateness of endovascular treatment of cerebral vasospasm after SAH.

Searches were performed using broad keyword phrases relating to the disease (cerebral vasospasm, delayed neurological deficit) and the procedure of

interest (eg, balloon angioplasty, intra-arterial, endovascular) in combination. Abstracts relevant to the specific question (in English or with English translation) were selected for further processing. Care was taken to ensure that duplicate or redundant references (eg, two papers on the same patient population) were not included. Once these criteria had been met, the remaining references were obtained in full text. Treatment and outcome data were compiled into tables 1 and 2 (available online only) and analyzed according to the guidelines for evidence based medicine proposed by the Stroke Council of the American Heart Association (AHA)[11] and the Centre for Evidence Based Medicine at the University of Oxford (http://www.cebm.net/index.aspx?o=1025).

### Transluminal balloon angioplasty

Table 1 (available online only) shows the data collected from searches specific to the *therapeutic* use of transluminal balloon angioplasty (TBA). This procedure is also used prophylactically, and these studies were not included in this analysis. Additionally, vasospasm following non-aneurysmal SAH was also excluded. More than 150 abstracts were filtered to extract the most pertinent and relevant studies, included in table 1 (available online only).

### Intra-arterial vasodilator infusion therapy

Table 2 (available online only) shows the data collected from searches specific to the *therapeutic* use of intra-arterial vasodilator infusion therapy (IAVT). Vasospasm following non-aneurysmal SAH was excluded. More than 200 abstracts were filtered to extract the most pertinent and relevant studies, included in table 2 (available online only).

## PREVENTIVE CARE

A comprehensive discussion of practices aimed at preventing PHCV in the SAH patient is beyond the scope of this document. Of the many methods employed, oral administration of nimodipine has the most evidence supporting it (Class 1, Level of Evidence A).[12] Early management of the ruptured aneurysm and maintenance of a normovolemic, normotensive state is classified as a Class IIa recommendation, Level of Evidence B, according to AHA guidelines.

The current literature does not support prophylactic invasive interventional therapies for PHCV. Interest in prophylactic TBA emerged from observations that clinical TBA would prevent recurrent or progressive constriction of treated vessels. This interest was supported by the results of animal studies that showed prevention of PHCV by prophylactic TBA in SAH models.[13] The first clinical pilot study of prophylactic TBA in selected patients at high risk for PHCV (Fisher grade 3) indicated a very high procedure related mortality of 8%; even more discouraging was the finding that 25% of surviving patients were dead or disabled at 3 months.[14] A subsequent phase II multicenter randomized controlled trial of prophylactic TBA in Fisher grade 3 patients showed no positive effect on outcome.[15] In contrast with therapeutic TBA, prophylactic TBA involves stretching the target vessel beyond its baseline resting caliber. Consequently, the risk of vessel rupture and the vascular response to injury may be distinct. These differences are suspected, accounting for the poor results of prophylactic TBA.

Currently practiced methods of IAVT involve either slow bolus administration of drug or prolonged infusions lasting approximately 30–90 min. Because the therapeutic effects of all IAVT procedures are transient, pre-emptive treatment of patients is not expected to prevent subsequent development of PHCV.

## MEDICAL MANAGEMENT

Medical therapies for PHCV are endorsed by the Stroke Council of the AHA as a Class IIa recommendation, Level of Evidence B. These therapies focus on augmentation of cerebral perfusion through an increase in mean arterial pressure and central venous pressures by intravascular volume expansion and intravenous administration of vasopressors. Additional hemodynamic therapies focused on increasing preload and decreasing blood viscosity have been described.[16] Specific recommendations for the medical management of PHCV were summarized in a recent consensus report from the Neurocritical Care Society.[16] In many patients, medical therapy will restore a compensated state of cerebral perfusion and reverse associated neurological deficits. Medical therapy is generally considered firstline management for PHCV as the treatment related risks are usually much lower than the risks of invasive interventional therapies. Exceptions may include PHCV in patients with unsecured ruptured aneurysms and patients with decompensated cardiac disease or intestinal ischemia. Although there is a significant risk of aneurysm rebleeding in patients with unsecured ruptured aneurysms, hypertensive therapy has not been associated with bleeding from unruptured aneurysms in SAH patients that have multiple aneurysms.[17 18] Patients with extensive myocardial infarction, decompensated heart failure or other cardiac disease may not tolerate aggressive medical therapy. Medical therapy may also be limited by specific complications, including intestinal ischemia.

## GENERAL INDICATIONS FOR INVASIVE INTERVENTIONAL MANAGEMENT

Invasive interventional management strategies should be considered in aneurysmal SAH patients with new neurological deficits suspected to be the result of PHCV when the deficits are not reversed or incompletely reversed by medical therapy. In a recent consensus statement published by the Neurocritical Care Society, an international multidisciplinary panel agreed that endovascular intervention for symptomatic vasospasm may be indicated when medical management has failed or there is a concern for complications from medical management.[19] With evidence that clinical improvement after endovascular therapy is most often achieved when treatment is initiated within 2 h of symptom onset, patients that are medically managed should be frequently reassessed.[20] If a satisfactory response to medical therapy is not realized within 1 h of initiation, the decision for interventional management should not be delayed. In patients with unsecured ruptured aneurysms, in whom aggressive medical therapy carries a high risk of rebleeding from the index lesion, local treatment of remote vascular territories by IAVT or TBA may have a role.[17 18] Interventional therapies should also be considered when medical therapy is contraindicated or beneficial to the patient but cannot be sustained because of cardiopulmonary, intestinal or other serious treatment related complications.

In many poor grade SAHs, it is difficult or impossible to clinically assess the patient's neurological deterioration. Consequently, it may be prudent to treat moderate to severe vasospasm revealed by non-invasive studies and confirmed by digital subtraction angiography (DSA). Transcranial Doppler studies and CT angiography are helpful in identifying patients with clinically silent PHCV. Cerebral perfusion imaging is being investigated as a diagnostic tool in this setting. Cerebral perfusion imaging is theoretically advantageous because it is sensitive to constriction of both proximal large vessels and small distal vessels.[21] Recent data suggest that severe angiographic cerebral

vasoconstriction, as determined by DSA, is an independent and reversible cause of cerebral infarction, neurological deterioration and poor clinical outcomes in SAH patients.[3 4] Thus angiographic cerebral vasoconstriction may be considered an indication for invasive interventional management when clinical indicators are not reliable.

## INVASIVE INTERVENTIONAL MODALITIES

Established interventional modalities for definitive treatment of patients with symptomatic PHCV include selective IAVT and TBA. Limited data on the use of aortic balloon catheters for augmentation of supra-aortic blood flow have been published, and objective determination of its proper role in the management of PHCV is not yet possible.[22] Emerging invasive treatment modalities outside the scope of this document include intrathecal vasodilator administration, topical administration of prolonged release vasodilators (nicardipine) and cisternal irrigation with thrombolytic agents.

### Transluminal balloon angioplasty

In the 1980s and early 1990s, reports of TBA for the treatment of PHCV began to appear.[23–25] Most early reports were based on the use of flow directed non-detachable silicone balloons with monopolar fixation, enabling balloon elongation in addition to radial expansion. Over the wire balloon angioplasty catheters with bipolar fixation have increasingly been used since the late 1990s and are currently the only available clinical devices.[26] Although over the wire catheter navigation has improved access to tortuous distal anatomy, anterior cerebral artery angioplasty remains technically challenging.

The mechanisms whereby TBA reverses the arterial narrowing of PHCV have not been completely elucidated. Evidence exists that balloon angioplasty inflicts a paralytic injury on cerebrovascular smooth muscle cells that prevents vasoconstriction. Although TBA does not typically cause gross disruption of the arterial wall, it does result in histologically evident alterations of the tunica intima and tunica media. Animal studies have confirmed microscopic disruption of connective tissue fibers in the extracellular matrix of the vessel wall and smooth muscle flattening.[27] TBA likely involves physical disruption of cellular contractile elements and/or their relationship to the extracellular matrix skeleton of the vessel. The process is likely mediated by forceful stretching of actively shortening muscle fibers. In theory, passive vessel relaxation against an expanding balloon may not achieve the same therapeutic effect. For this reason, many neurointerventionists believe that TBA is most effective if it is performed before the administration of intra-arterial vasodilators. In practice, however, it is sometimes necessary to prepare a vessel for TBA by initially performing IAVT if the vessel lumen is insufficient to permit microguidewire navigation or balloon introduction.

### Intra-arterial vasodilator infusion therapy

A variety of vasodilators have been directly infused into the cerebral arterial circulation through transarterial catheters to treat patients with PHCV. Clinically relevant agents include phosphodiesterase inhibitors (papaverine and milrinone) and calcium channel blockers (nimodipine, verapamil, nicardipine). All of these agents presumably exert a reversible effect on the contractile apparatus of cerebrovascular smooth muscle cells causing relaxation and vasodilatation. Since PHCV is characteristically a self-resolving monophasic process, permanent alteration of vessel structure is not essential for successful therapy. The timing and magnitude of the vasodilatory response has not been completely characterized for any of the agents used in clinical practice. Early clinical studies indicated that papaverine improved cerebral blood flow for periods not longer than 3 h.[28] Newer agents, such as verapamil and nicardipine, may improve cerebral blood flow for longer periods, but the effects are still transient. Animal studies with intra-arterial verapamil demonstrate that drug induced cerebral vasodilatation develops gradually and stabilizes after an average of 15–30 min.[29] Clinical studies have shown that verapamil induced cerebral vasodilatation is not angiographically demonstrated after 5 min but is present after 10–15 min.[30 31] No angiographic data exist on the duration of the vasodilatory effect. Nonetheless, there is evidence that the effect of high dose intra-arterial verapamil on cerebral hemodynamics and brain metabolism may last as long as 12 h.[32]

## PREPARATION FOR INVASIVE INTERVENTIONAL THERAPIES

The population at risk for PHCV includes all patients with aneurysmal SAH. As above, risk can be further stratified by the amount of blood entering the subarachnoid space.[6 7] The development of a new focal neurological deficit or a generalized decline in neurological function (level of consciousness) in any patient who has suffered an aneurysmal SAH should prompt consideration of PHCV as a cause. However, it must be kept in mind that focal changes in the neurological examination also may be due to rebleeding from the aneurysm, seizures, infection, complications of aneurysm therapy or complications of ventricular drain placement. Non-focal changes in the neurological examination or worsening of a pre-existing neurological deficit may also be due to fever, infection, seizures, respiratory failure, hypoglycemia, electrolyte abnormalities, myocardial infarction or hydrocephalus. Transcranial Doppler (TCD) studies can be used to identify patients with PHCV. Non-contrast CT examination of the head should be obtained to exclude new intracranial hemorrhages and determine the location and extent of irreversible cerebral infarction. CT angiography and CT perfusion have been used by some authors to guide management of PHCV patients.[33] The specific role of these imaging modalities in the setting of PHCV has not been defined and a complete discussion is beyond the scope of this document. Although DSA is the diagnostic gold standard for PHCV, it is generally only indicated when a determination has been made that an invasive interventional management strategy will be pursued.

Once it has been determined that invasive interventional management of a patient with PHCV is indicated, the patient should be prepared for neuroangiography. Because the patient must lie flat on the neuroangiography table for a prolonged period of time, intracranial hypertension should be well controlled before transporting the patient from the intensive care unit. Furthermore, the potential for some interventional therapies to significantly increase intracranial pressure should be anticipated.[32] Cerebral ventricular drains are useful both to monitor and treat intracranial hypertension in this setting. Monitoring of intracranial pressure should be strongly considered when multiple vascular territories are being treated by IAVT.[34 35] Some interventional therapies may inadvertently lower systemic blood pressure and negatively impact cerebral perfusion.[32 36] Consequently, a functional arterial line should be in place for continuous blood pressure monitoring in the neuroangiography suite. Adequate intravenous access should be secured for the administration of sedatives, analgesics, vasopressors, anticoagulants and emergency drugs, including protamine.

The safety of intracranial TBA is increased if any voluntary or involuntary patient motion is eliminated. Consequently, if TBA is to be performed, general anesthesia should be strongly considered. If anesthesia is unavailable, mechanically ventilated patients may be sedated and chemically paralyzed to facilitate safe procedural conduct; it is advantageous to secure the necessary medications in advance. Patients should be well hydrated to minimize the nephrotoxic effects of iodinated contrast media and optimize hemodynamic factors for cerebral perfusion.

Before initiating definitive interventional treatment of PHCV, it is necessary to establish the angiographic diagnosis by DSA. Angiographic findings of cerebral vasospasm include loss of luminal caliber, increased cerebral circulation time and retrograde filling of cortical branch arteries in the affected territories. If a baseline cerebral angiogram is not available for comparison, it may be difficult to determine the severity of vasospasm. In such cases, the normal baseline arterial caliber is indeterminate and TBA may carry an excessive risk. This is especially true for arterial segments prone to congenital hypoplasia such as the A1 segment of the anterior cerebral artery and P1 segment of the posterior cerebral artery.

The invasive interventional treatment plan should be guided by the findings of DSA. The initiation of an invasive interventional treatment strategy requires DSA confirmation of the PHCV diagnosis. It is further necessary to delineate the involved arterial segments, assess the magnitude of vasoconstriction in both proximal and distal territories, and determine whether the affected vascular territory can be safely reperfused based on correlation with brain imaging studies.

## MODALITY ORIENTED INDICATIONS

### Transluminal balloon angioplasty

When invasive interventional management of PHCV is indicated, TBA may be considered for the treatment of large artery spasm within or proximal to the circle of Willis. Suitable vessels include the intradural vertebral arteries, basilar artery, intra-dural carotid arteries, M1 segments, A1 segments and P1 segments. Although there are reports of balloon angioplasty for distal arterial spasm (A2, A3, M2, P2 and posterior communicating artery), the data are limited and further study is necessary to establish the safety of this approach.[37] One major advantage of balloon angioplasty is that its therapeutic effect is generally sustained and retreatment is rarely necessary. Additionally, it does not increase intracranial pressure even when multiple vessels are treated.

In order to justify the procedural risks of TBA, a hemodynamically significant narrowing, or >50% reduction of the target vessel luminal diameter, must be demonstrated by DSA. This angiographic determination is most accurate when one can compare the study with the baseline pre-vasospasm angiogram. In general, if a baseline angiogram is not available for comparison, the magnitude of vasoconstriction cannot be reliably determined and the safety of TBA is questionable. This is especially true for the A1 segment of the anterior cerebral artery and the P1 segment of the posterior cerebral artery where congenital hypoplasia is very common. Furthermore, fenestrated vessels in severe spasm may appear to have a single lumen, and failure to recognize the fenestration because a baseline cerebral angiogram was not available can lead to over dilation with vessel rupture or other catastrophic injury.

Some authors have reported that small to moderate sized CT hypodensities may resolve after cerebral reperfusion by TBA.[38] Nevertheless, completed infarctions involving a large territory of the index vessel should discourage attempts to restore tissue perfusion as the risk of reperfusion hemorrhage may outweigh any clinical benefits. Fatal reperfusion hemorrhages after TBA for PHCV have been reported to occur up to 24 h after treatment.[39]

### Intra-arterial vasodilator infusion therapy

IAVT may be performed to treat PHCV—that is, confirmed by DSA—in patients who meet the indications for invasive interventional management. IAVT can be safely administered to treat spasm of cerebral arteries regardless of their size and position in the arterial tree. Because the risks of over dilation and vessel rupture are irrelevant for IAVT, the application of vasoconstriction thresholds relative to an angiographic baseline is more flexible. IAVT can be used together with TBA as a complementary treatment to address distal spasm after proximal spasm has been treated by TBA, or IAVT can be used as a standalone therapy to manage both proximal and distal cerebral vasospasm. Currently used methods for IAVT include bolus injections or brief infusions over a period of approximately 30–90 min. Disadvantages of currently used IAVT techniques include delayed onset of action, temporary therapeutic effect and the possibility of intracranial hypertension when multiple vascular territories are treated.

## MODALITY SPECIFIC PROCEDURAL SAFETY

### Transluminal balloon angioplasty

Complications of TBA for cerebral vasospasm include vessel perforation (with microguidewire, microcatheter or balloon), vessel rupture (balloon), index artery dissection, index artery occlusion, ischemic stroke, hemorrhagic transformation of infarcted tissue, rebleeding from uncontrolled aneurysms and displacement of aneurysm clips.

Cerebral arterial rupture from over dilation is often lethal and most survivors have very poor clinical outcomes. The rate of cerebral arterial rupture in large case series has been reported to be as high as 4–5%.[24] Contemporary estimates based on literature review suggest that the rupture rate is closer to 1% using modern devices and techniques.[40]

Estimation of the true incidence of procedure related ischemic stroke in patients undergoing TBA is difficult because cerebral infarctions that are caused by the effects of PHCV alone are difficult to distinguish from those that are iatrogenic. Nevertheless, thromboembolic complications have been reported in as many as 4–5% of cases.[26]

The long term angiographic results of TBA for PHCV have not been systematically evaluated. Long term development of flow limiting stenoses at the angioplasty site has been reported.[41] The true incidence and prevalence of steno-occlusive sequelae due to intimal hyperplasia or dissection is unknown.

The risk of specific complications is modified to a significant degree by anatomical factors, disease related factors and technical factors. As with all surgical procedures, the physician should make every effort to minimize the risk of procedure related complications.

The target vessel selected for TBA represents one of the most important anatomical factors governing procedure related risk. PHCV frequently involves the large conducting subarachnoid arteries within and proximal to the circle of Willis at the base of the brain. These proximal cerebral vessels are often large with normal luminal calibers that range from 2 to 5 mm. Most clinical experience with TBA for PHCV has been restricted to these

large proximal cerebral vessels (intracranial internal carotid artery, vertebral artery, basilar artery, M1, A1 and P1). Due to their small size and relative mural frailty, it is unclear to what extent the more distal vessels can be safely dilated with currently available balloon angioplasty catheters. It is not advisable to treat spastic vessels with baseline luminal diameters <1.5 mm by balloon angioplasty.

Technical factors that modify procedural risks relate to the use of anticoagulation. Intravascular stasis of blood, endothelial injury and a large profile intravascular foreign body surface are all factors that promote cerebral thromboembolism in this setting. Consequently, it is important to confirm effective anticoagulation before placing instrumentation in the spastic cerebral arteries with a guidewire or angioplasty balloon. In general, heparin is used because of its rapid onset of action, short half-life and ease of reversibility with protamine. An activated clotting time of 250–300 s is generally desirable. In theory, the risks of procedure related complications during microguidewire navigation and balloon inflation increase if the patient is moving. Consequently, most operators feel that procedural safety is optimized if patients are mechanically ventilated and paralyzed during TBA. Patient paralysis maximizes visibility of very small angioplasty balloons, and allows high quality digital subtraction angiograms to guide therapeutic decision making.

TBA for PHCV is currently performed with commercially available single and double lumen over the wire balloon catheters that track over 0.010 inch and 0.014 inch microguidewires, respectively. Coaxial navigation and balloon inflation can be safely performed using roadmap and fluoroscopic guidance. Control angiograms, performed through the guiding catheter after each balloon inflation cycle, provide important angiographic feedback to the operator. While single lumen balloon catheters are all compliant, double lumen balloon catheters may be compliant, semi-compliant or non-compliant.

It is prudent to under size balloons relative to the baseline normal vessel diameter (≤80–85%) to avoid over dilation. If possible, successive dilations are performed from distal to proximal to avoid crossing a fresh angioplasty site with balloon or wire, as this may inadvertently raise a dissection flap.

If possible, balloon length should be chosen to cover the longest contiguous straight segment of vessel to be treated, so that multiple dilations will not be necessary. When single lumen balloon occlusion microcatheters are subjected to multiple inflations, blood entering the balloon through the distal endhole can diminish balloon radio-opacity, decreasing the safety of inflation under fluoroscopic guidance and preventing timely balloon deflation. If the target segment is contiguous around a sharply angulated curve, a shorter balloon may be chosen and serial distal to proximal dilations performed to avoid forced straightening of the artery when the balloon is inflated. The limits of balloon inflation are determined by direct observation of balloon size and shape fluoroscopically, in addition to tracking the calculated inflation volumes.

Angioplasty can be safely performed using compliant, semi-compliant and non-compliant balloons. Most double lumen balloon catheters suitable for intracranial angioplasty are designed for the treatment of coronary artery atherosclerotic vascular disease. These balloons reach nominal diameters at pressures in the range of 6–18 atmospheres. Generally, a much lower balloon pressure is needed to counter the contractile force generated by a cerebral artery in spasm, and restore normal luminal caliber. The critical threshold for vessel rupture is determined by vessel radius and wall tension, rather than balloon pressure. When a non-compliant balloon bridges mismatched arterial segments, the relatively rigid balloon will disproportionately stretch the smaller segment. The smaller segment will be at greatest risk of rupture. When a compliant balloon bridges mismatched arterial segments, the balloon will preferentially expand into the larger segment. This results because at the same balloon pressure a higher wall tension is required to resist balloon expansion in the larger segment according to Laplace's law. Consequently, the larger caliber segment is at greatest risk of rupture. Balloon inflation should be limited to approximately 85% of the baseline luminal diameter of any target segment.

Disease related factors that modify procedural risks encompass both end organ disease and vessel wall disease. Reperfusion of completed cerebral infarctions can lead to significant neurological deterioration owing to hemorrhagic transformation. Consequently, it is inadvisable to perform TBA of vessels supplying the territory of a large completed cerebral infarction. TBA performed adjacent to clipped ruptured aneurysms has been associated with fatal rupture of the parent artery. Angioplasty of vessel segments that may be structurally compromised should be avoided.

### Intra-arterial vasodilator infusion therapy

IAVT can be administered through selective (≥4 French) or superselective (≤3 French) transarterial catheters. Infusions given through superselective microcatheters placed within affected pial arteries ensure that an effective dose is delivered to the target circulation. This may be advantageous in specific situations where two circulations are competing for flow at a bifurcation. For example, if the intent is to treat anterior cerebral artery spasm in the setting of a tightly constricted A1 and widely patent M1, drug administered into the internal carotid artery would run off to the lower resistance middle cerebral artery circulation substantially reducing the dose delivered to the anterior cerebral artery. Another specific example in which superselective infusion is advantageous relative to selective infusion relates to the risk of transient and permanent blindness as a result of papaverine infusion into the internal carotid artery. There is evidence that the risk is significantly higher when papaverine infusions are given through catheters placed proximal to the ophthalmic artery. In many patients, however, effective treatment can be administered by infusing vasodilators through selective catheters positioned in the extracranial internal carotid artery or vertebral artery. Vasodilators infused into the cerebral arterial circulation in this way can produce vasodilatation at all levels of the cerebral arterial tree without the associated risks of pial vessel instrumentation. In theory, continuous infusions delivered at a constant rate may be asymmetrically distributed to downstream vascular territories when flow is laminar. Consequently, some operators administer infusions as a series of rapid pulsatile bursts to ensure uniform dispersal of drug in the anterograde bloodstream. IAVT procedures are safe for the management of PHCV involving the distal cerebral arteries beyond the circle of Willis, a commonly encountered problem. In addition, IAVT can be safely performed in awake patients that are independently breathing. Nevertheless, IAVT procedures are not without risk. The procedure related risks encompass all the risks of DSA, including the small risk of cervicocerebral arterial dissection and stroke. Treatment specific risks depend to some degree on the vasodilator agent selected. All agents have occasionally been associated with seizures, intra-cranial hypertension and systemic hypotension. The onset of action for intra-arterial vasodilators is often delayed and the therapeutic effects are short lived. Consequently,

repeated procedures are often necessary to manage relapsing symptoms with the cumulative risks accruing over time.

For more than 20 years, papaverine, a phosphodiesterase inhibitor, was the most widely used agent employed in IAVT procedures. It is infrequently used in current clinical practice because of concerns about the potential neurotoxicity of papaverine or its commonly used preservative chlorobutanol.[42] These concerns were sparked by a report documenting the development of symptomatic brain lesions in five patients treated with intra-arterial papaverine for PHCV in San Francisco when all patients became symptomatic immediately after the initiation of intra-arterial papaverine and all developed gray matter lesions in the irrigated vascular territories on brain MRI. Histological findings in one patient were consistent with selective gray matter necrosis, a feature more closely associated with the effect of metabolic toxins rather than ischemic tissue damage. Intra-arterial papaverine is commonly administered in normal saline as a 0.3% solution at a dose of 300 mg per arterial territory infused over a 30 min period. Compared with other vasodilators used for the treatment of PHCV, papaverine is much more insoluble and has a strong tendency for precipitation in aqueous solutions. Mixing of papaverine solutions with iodinated contrast or heparin solutions may promote precipitation. The formation of insoluble crystals in clinical preparations of papaverine can lead to clinically significant embolic complications.[43] Intracranial hypertension has been reported to be a significant problem after treatment of multiple vascular territories by intra-arterial papaverine infusion.[34] This presumably occurs due to the augmentation of cerebral blood volume produced by widespread cerebral vasodilatation. Seizures, mydriasis and transient hemiparesis have also been reported. Transient and rarely permanent monocular blindness has been reported after intra-arterial papaverine infusion through catheters placed in the internal carotid artery proximal to the origin of the ophthalmic artery. Cardiac dysfunction and respiratory arrest have been reported with posterior circulation infusions of papaverine. Milrinone, another phosphodiesterase inhibitor, has been used for IAVT in small case series.[44]

Calcium channel blockers have been infused directly into the cerebral arteries to treat PHCV. Nimodipine was the first agent used in this way. The use of intra-arterial verapamil and nicardipine are being increasingly reported in the literature. Verapamil is typically administered as a bolus infusion whereas nicardipine is delivered slowly in a prolonged infusion for up to 90 min periods. Prolonged infusions involving indwelling transarterial catheters are theoretically associated with a greater risk of thromboembolism. Although there are reports of prolonged infusions through transarterial intracranial microcatheters lasting as long as 20 h (median 8 h), further study is necessary to establish the safety of this approach.[45] Significant increases in intracranial pressure and decreases in cerebral perfusion pressure lasting for several hours have been reported with high dose intra-arterial verapamil infusion.[32] Systemic hypotension is rarely seen with verapamil; however, doses exceeding 35 mg per procedure have been associated with significant decreases in mean arterial pressure, often in delayed fashion as long as 5–7 h after the procedure.[32] Intra-arterial nicardipine is more often associated with hypotension, particularly with high doses.[36 46 47] Initial reports of intra-arterial verapamil described doses of 2–5 mg per vessel treated. Although many operators currently use 10–20 mg per vessel, little is known about the dose–response relationship. We have observed seizures in patients treated with high doses of intra-arterial verapamil (≥15 mg/vessel). High dose intra-arterial verapamil has also been associated with hypotension in more than 50% of patients.[32] Nicardipine has been given in doses of 0.5–0.6 mg per vessel but doses higher than 15 mg per vessel are also reported.[36]

## PARADIGM AND MODALITY SPECIFIC PROCEDURAL EFFICACY

### An invasive interventional therapy paradigm

The invasive interventional therapy (IIT) paradigm encompasses the selective application of two different treatment modalities according to the basic principles outlined in this document, TBA and IAVT. Although the two modalities differ significantly and warrant careful scrutiny of their risks and benefits independently, in clinical practice they are often employed in complementary fashion as individual components of an integrated treatment plan. At the time of this writing, no randomized controlled trials examining the technical or clinical efficacy of the IIT paradigm were published. Nevertheless, the preliminary results of such a trial were presented at the 2011 International Conference on Neurovascular Events after Subarachnoid Hemorrhage (Cincinnati, Ohio, USA).[48] The preliminary data for the first 21 patients randomized (11 to medical management vs seven to IIT) show no significant difference in the rate of DCI related cerebral infarctions between the two groups. The 6 month clinical outcome data for the two groups are pending. This multicenter international European trial is currently enrolling patients and it is hoped that the results will add to our understanding of the IIT paradigm, and its proper role in the management of patients with PHCV.

### Transluminal balloon angioplasty

There are no randomized clinical trials demonstrating the technical or clinical efficacy of TBA. All current literature is based on self-reported case series. The technical efficacy of TBA reversing cerebral vasoconstriction in patients with PHCV is in the 80–100% range.[39 49–51] Clinical series have reported improvements in TCD velocities, luminal caliber assessed by DSA and cerebral blood flow.[52 53] More importantly, it has been demonstrated that TBA reduces neurological deficits in patients with PHCV and that early treatment (<2 h from symptom onset) significantly increases the probability of sustained clinical improvement.[20 39 49 51 54]

Technically successful restoration of normal or near normal luminal caliber is achieved in the majority of TBA procedures. Case series report angiographic improvement in 82–100% of patients. On the other hand, clinical success varies widely, with reversal of DCI in 31–77% of patients.[39 53 55 56] This wide range of clinical success partly reflects differences in severity of illness and reporting bias. Furthermore, differences in the timing of intervention may underlie differences in the rate of clinical improvement. In one study, 70% of patients treated by balloon angioplasty within 2 h of symptom onset clinically improved; however, those treated later clinically improved in only 40% of cases.

### Intra-arterial vasodilator infusion therapy

Studies of IAVT using papaverine demonstrate technical efficacy (angiographic improvement) in 60–90% of cases.[57–59] Unfortunately, most of these studies show clinical improvement in only 25–50% of treated patients.[57 59 60] In one case control series, no difference in outcome was found between papaverine treated patients (45% favorable outcomes) and control medically managed patients (58% favorable outcomes).[61] Studies of IAVT with the phosphodiesterase inhibitor milrinone have shown angiographic improvement and increases in cerebral blood flow, but clinical improvement has not been documented.[44 62]

The vast majority of published data on IAVT with calcium channel blockers are based on single or multiple treatments using pulse dose administration. Studies of intra-arterial nimodipine for PHCV have shown angiographic improvement in up to 43% of procedures and clinical improvement in 76% of treated patients.[63] Studies of intra-arterial verapamil have also shown evidence of modest angiographic improvement with an average increase in vessel diameter of 29–44%.[30 64] The magnitude of vessel response is proportional to the severity of angiographic vasoconstriction.[64] Treatment effect is similar for large proximal vessels and small distal branches, and there is no difference between the anterior circulation and posterior circulation. Unfortunately, only 29% of patients solely treated by verapamil IAVT have shown clinical improvement.[30] Reported data for IAVT with nicardipine indicate angiographic improvement in all treated patients but clinical improvement in only 42%.[65] Improved clinical outcomes have been reported with high dose nicardipine IAVT although larger effects on systemic blood pressure have been noted.[47]

## SUMMARY OF EVIDENCE AND RECOMMENDATIONS

### Transluminal balloon angioplasty

There is evidence from uncontrolled clinical case series demonstrating the safety and technical efficacy of TBA in reversing moderate to severe angiographic constriction of the large proximal cerebral arteries (≥2 mm luminal diameter) and in augmenting cerebral blood flow in patients with PHCV. Additional evidence from uncontrolled clinical case series show that short term clinical improvement is seen in the majority of symptomatic patients. The data suggest that the probability of clinical improvement is maximized if treatment is administered early (<2 h from onset of symptoms). There is no significant evidence that the intervention results in better long term clinical outcomes relative to medical management. Consequently, we conclude that TBA may be beneficial and may be considered for flow limiting PHCV involving the proximal intradural cerebral arteries (ICA, M1, VA, basilar artery, A1, P1) symptomatic with cerebral ischemia and refractory to maximal medical therapy. We regard this as a Class IIb (size of treatment effect), Level B (level of certainty) intervention according to guidelines published by the Stroke Council of the AHA.[11] According to guidelines provided by the University of Oxford, Centre for Evidence Based Medicine, we classify this as a Level 4, Grade C intervention (http://www.cebm.net/index.aspx?o=1025).

### Intra-arterial vasodilator infusion therapy

There is evidence from uncontrolled clinical case series demonstrating variable safety and variable technical efficacy for pulse dose intra-arterial calcium channel blocker (nimodipine, verapamil or nicardipine) infusions in reversing angiographic vasoconstriction in patients with PHCV. Safety and technical efficacy depend on the agent and the administered dose. Treatment effect is similar at all levels of the cerebral arterial tree in both the anterior and posterior cerebral circulation. Uncontrolled case series demonstrate clinical improvements in a variable percentage of patients depending on the agent used, the dose administered and the timing of intervention. There are no randomized controlled studies that address clinical outcomes. Consequently, we conclude that pulsed dose intra-arterial calcium channel blocker infusions may be beneficial and may be considered for symptomatic PHCV refractory to maximal medical therapy. We regard this as a Class IIb recommendation that is supported by Level of Evidence B according to AHA guidelines.[11] According to the University of Oxford, Centre for Evidence Based Medicine, we classify this as a Level 4, Grade C intervention (http://www.cebm.net/index.aspx?o=1025). Papaverine IAVT has been associated with significant complications, and case series have not shown convincing evidence of a treatment related clinical benefit. Consequently, we conclude that papaverine IAVT should not be administered to treat PHCV. We classify this as a Class III, Level of Evidence B intervention according to AHA guidelines.[11] According to the University of Oxford Centre for Evidence Based Medicine guidelines, this recommendation is Level 4, Grade C.

### Proposed reporting standards for clinical practice and future clinical studies

Our objective was to assess the published literature for evidence supporting a particular therapeutic intervention for a set of specific indications. The approach has become commonplace given the increasing importance of practicing evidence based medicine in the modern world. In the course of this effort, our ability to extract meaningful data from multiple publications involving diverse patient populations and varied treatment protocols relied on the use of terms, definitions and scales that have universal meaning (reporting standards). The application of reporting standards in published clinical studies allows other researchers to unambiguously interpret and classify results into data silos that have matched characteristics. The implementation of reporting standards in routine clinical practice enables varied practitioners from the same or different institutions to pool their material into large datasets with increased statistical power. Efforts to develop such data repositories by researchers who study PHCV are currently underway. The formation of the Subarachnoid Hemorrhage International Trialists Repository was announced at the 2011 International Conference on Neurovascular Events after Subarachnoid Hemorrhage in Cincinnati, Ohio, USA. The primary objective of this consortium is to develop and validate outcome prediction tools that integrate widely accepted reporting standards. The consortium represents an important model for future research efforts and will be managed through the Division of Neurosurgery at St Michael's Hospital, Toronto, Ontario, Canada.

Standard definitions for DCI and PHCV were recently addressed by an international ad hoc panel of leading experts in SAH research.[66] Their definitions emphasize DCI as an end organ phenomenon requiring evidence of functional neurological impairment on physical examination (new focal deficit or change in Glasgow Coma Score) or evidence of cerebral infarction on brain imaging studies (CT or MRI) or autopsy. The definition does not specify pathogenesis and is not tied to vascular imaging findings. This approach emphasizes that secondary brain injury in patients with aneurysmal SAH may also involve microvascular dysfunction and cortical spreading depolarization to varying degrees. This concept is supported by the results of recent drug trials which show significant reduction in the occurrence of angiographic vasospasm without measurable improvements in clinical outcome.[67] Vergouwen *et al* recognize that clinical deterioration caused by DCI is difficult to ascertain given the multitude of other factors that are often contributory.[66] They propose that any focal neurological deficit or a decrease of ≥2 points on the Glasgow Coma Scale, lasting for at least 1 h, can be attributed to DCI if the changes are not immediately present after therapeutic occlusion of the aneurysm and if they are sustained for at least 1 h. Additionally, the deficits cannot be attributable to other causes based on clinical, neuroimaging or laboratory assessment. According to the definition,

DCI related infarctions are demonstrated by CT or MRI within 6 weeks of the ictus but are not present at 24–48 h after aneurysm occlusion. Neuroimaging evidence of cerebral infarction (CT or MRI) and functional outcome (modified Rankin or Glasgow Outcome Score) are favored as the main endpoints for future studies given the relatively high interobserver agreement rates. Vergouwen *et al* strongly recommend that the term 'vasospasm' (PHCV) is reserved for arterial narrowing demonstrated on DSA, CT angiography or MR angiography .[66] They conclude that TCD is insufficient diagnostic proof of 'vasospasm' given its poor sensitivity and specificity.

In this standards document we propose additional reporting standards that are relevant to the diagnosis and management of PHCV after aneurysmal SAH. These standards address clinical grading of DCI, angiographic grading of PHCV; treatment related technical factors; response to treatment (clinical and angiographic); and outcome measures (clinical and imaging).

Vergouwen *et al* established a working definition of DCI and related cerebral infarctions that will serve as the foundation of our proposed reporting standards. With the clinical severity of DCI varying over a wide range, a clinical grading system is regarded as a useful descriptor. Toward that end, we propose that the severity of neurological impairment resulting from DCI is expressed quantitatively using the National Institutes of Health Stroke Scale score or the Glasgow Coma Scale. In both cases, the deficit can be quantified as a numerical change from baseline. This approach will allow comparison of patient subgroups that are equally compromised by DCI.

Reporting standards for the angiographic grading of PHCV should apply uniform diagnostic criteria that are concise and objective. At a minimum, it is necessary to describe location and magnitude. Specification of location should include the name of the affected vessel (ie, internal carotid artery, middle cerebral artery, basilar artery, etc) and the segment of the affected vessel (ie, ophthalmic segment of internal carotid artery, M1, A1). Further description of the length of the affected vessel segment may be considered: avoid subjective terms and specify length in millimeters. The magnitude of PHCV should be reported as a discrete per cent reduction in luminal diameter or using a quartile system for this endpoint: grade one 0–25% (mild); grade two 26–50% (moderate); grade three 51–75% (severe); grade four >75% (critical).

Technical reporting standards for TBA should address the location of the vessel segment treated and the devices used to perform the treatment (microguidewires, balloon catheters and inflation devices). Inflation endpoints should be described in terms of balloon diameter, volume or pressure. Technical reporting standards for IAVT should include the agent infused, the total dose infused, the method and duration of infusion, as well as the catheter and catheter position used for infusion. The timing of post-treatment control angiograms should be reported. When control or follow-up angiograms are performed, technical results should be reported as a percentage gain in luminal diameter. Major and minor procedure related complications, including any related morbidity and mortality, should be clearly reported as such.

Reporting standards for clinical response to treatment should mirror the scales used to report the clinical severity of DCI. That is, the response to treatment should be quantified as a numerical increase in the patient's National Institutes of Health Stroke Scale score or the Glasgow Coma Scale. Likewise, the angiographic response to treatment should be quantified for each affected location as a complete response (no residual spasm), partial response or no response. In cases of partial response the residual spasm relative to baseline should be estimated according to the quartile scale described above.

In the interest of uniformity and reproducibility, clinical outcome should be reported using the Glasgow Outcome Scale. Clinical outcomes in the current PHCV literature are most commonly reported using the Glasgow Outcome Scale and future studies should strive for uniformity with precedent studies.[20 23 25 30 38 39 47 49 52 55 57 59 60 63 65 68–71] The modified Rankin Scale is a suitable but less desirable alternative. Some experts have suggested that the failure of several therapeutic trials for PHCV may be related to the inability of commonly used outcome scales to detect moderate to severe degrees of cognitive dysfunction after aneurysmal SAH. For this reason, domain specific neuropsychiatric testing has been advocated as an additional clinical outcome measure by some. The length of follow-up (in months) used for determination of clinical outcomes should be clearly expressed.

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## REFERENCES

1. **Egge A,** Waterloo K, Sjoholm H, *et al*. Prophylactic hyperdynamic postoperative fluid therapy after aneurismal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. *Neurosurgery* 2001;**49**:593–605.
2. **Turjman J,** Mimon S, Yilmaz H. Epidemiology, clinical study and pathology of vasospasm. *J Neuroradiol* 1999;**26**:S10–16.
3. **Crowley RW,** Medel R, Dumont AS, *et al*. Angiographic vasospasm is strongly correlated with cerebral infarction after subarachnoid hemorrhage. *Stroke* 2011;**42**:919–23.
4. **Vergouwen MDI,** Ilodigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. *Stroke* 2011;**42**:924–9.
5. **Clark JF,** Sharp FR. Bilirubin oxidation products (BOXes) and their role in cerebral vasospasm after subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 2006;**26**:1223–33.
6. **Fisher CM,** Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery* 1980;**6**:1–9.
7. **Kistler JP,** Crowell RM, Davis KR, *et al*. The relation of cerebral vasospasm to the extent and location of subarachnoid blood. *Neurology* 1983;**33**:424–36.
8. **Heros RC,** Zervas NT, Varsos V. Cerebral vasospasm after subarachnoid hemorrhage: an update. *Ann Neurol* 1983;**14**:599–608.
9. **Kassell NF,** Sasaki T, Colohan AR, *et al*. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke* 1985;**16**:562–72.
10. **Zabramski JM,** Hamilton MG. Cerebral vasospasm. In: Carter LP, Spetzler RF, Hamilton MG, eds. *Neurovascular surgery*. New York: McGraw Hill, 1995:583–601.
11. **Meyers PM,** Schumacher HC, Higashida RT, *et al*. Indications for the performance of intra-cranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Interdisciplinary Council on Peripheral Vascular Disease and Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation* 2009;**119**: 2235–49.
12. **Bederson JB,** Connolly ES, Batjer HH, *et al*. Guidelines for the management of aneurismal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 2009;**40**:994–1025.
13. **Megyesi JF,** Findlay JM, Vollrath B, *et al*. In vivo angioplasty prevents the development of vasospasm in canine carotid arteries. Pharmacological and morphological analyses. *Stroke* 1997;**28**:1216–24.
14. **Muizelaar JP,** Zwienenberg M, Rudisill RN, *et al*. The prophylactic use of transluminal balloon angioplasty in patients with Fisher Grade 3 subarachnoid hemorrhage: a pilot study. *J Neurosurg* 1999;**91**:51–8.
15. **Zwienenberg-Lee M,** Hartman J, Rudisill N, *et al*; for The Balloon Prophylaxis for Aneurysmal Vasospasm (BPAV) Study Group. 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* 2009;**39**:1759–65.

16. **Diringer MN,** Bleck TP, Hemphill JC, *et al*. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care* 2011;**15**:211—40.
17. **Kassell NF,** Peerless SJ, Durward QJ, *et al*. Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. *Neurosurgery* 1982;**3**:337—43.
18. **Platz J,** Guresir E, Vatter H, *et al*. Unsecured intracranial aneurysms and induced hypertension in cerebral vasospasm: is induced hypertension safe? *Neurocrit Care* 2011;**14**:168—75.
19. **Kimball MW,** Velat GJ, Hoh BL; The participants in the international mult-disciplinary consensus conference on the critical care management of subarachnoid hemorrhage. Critical care guidelines on the endovascular management of cerebral vasospasm. *Neurocrit Care* 2011;**14**:336—41.
20. **Rosenwasser RH,** Armonda RA, Thomas JE, *et al*. Therapeutic modalities for the management of cerebral vasospasm: timing of endovascular options. *Neurosurgery* 1999;**44**:975—80.
21. **Wintermark M,** Dillon WP, Smith WS, *et al*. Visual grading system for vasospasm based on perfusion CT imaging: Comparisons with conventional angiography and quantitative perfusion CT. *Cerebrovasc Dis* 2008;**26**:163—70.
22. **Lylyk P,** Vila JF, Miranda C, *et al*. Partial aortic obstruction improves cerebral perfusion and clinical symptoms in patients with symptomatic vasospasm. *Neurol Res* 2005;**27**(Suppl 1):S129—35.
23. **Eskridge JM,** McAuliffe W, Song JK, *et al*. Balloon angioplasty for the treatment of vasospasm: results of first 50 cases. *Neurosurgery* 1998;**42**:510—17.
24. **Eskridge JM,** Song JK. A practical approach to the treatment of vasospasm. *AJNR Am J Neuroradiol* 1997;**18**:1653—60.
25. **Zubkov YN,** Nififorov BM, Shustin VA. Balloon catheter technique for dilatation of constricted cerebral arteries after aneurismal SAH. *Acta Neurochir* 1984;**70**:65—79.
26. **Terry A,** Zipfel G, Milner E, *et al*. Safety and technical efficacy of over-the-wire balloons for the treatment of subarachnoid hemorrhage induced cerebral vasospasm. *Neurosurg Focus* 2006;**21**:1—7.
27. **Yamamoto Y,** Smith RR, Bernanke DH. Mechanism of action of balloon angioplasty in cerebral vasospasm. *Neurosurgery* 1992;**30**:1—6.
28. **Voldby B,** Enevoldsen EM, Jensen FT. Cerebrovascular reactivity in patients with ruptured intracranial aneurysms. *J Neurosurg* 1985;**62**:59—67.
29. **Shimizu K,** Ohta T, Toda N. Evidence for greater susceptibility of isolated dog cerebral arteries to calcium antagonists than peripheral arteries. *Stroke* 1980;**11**:261—6.
30. **Feng L,** Fitzsimmons B, Young W. Intra-arterially administered verapamil as adjunct therapy for cerebral vasospasm: safety and a two year experience. *AJNR Am J Neuroradiol* 2002;**23**:1284—90.
31. **Mazumdar A,** Rivet DJ, Derdeyn CP, *et al*. Effect of intra-arterial verapamil on the diameter of vasospastic intracranial arteries in patients with cerebral vasospasm. *Neurosurg Focus* 2006;**21**:E15.
32. **Stuart RM,** Helbok R, Kurtz M, *et al*. High-dose intra-arterial verapamil for the treatment of cerebral vasospasm: prolonged effects on hemodynamic parameters and brain metabolism. *Neurosurgery* 2011;**68**:337—45.
33. **Binaghi S,** Colleoni ML, Maeder P, *et al*. CT angiography and perfusion CT in cerebral vasospasm after subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 2007;**28**:750—8.
34. **Andaluz N,** Tomsick TA, Tew JM, *et al*. Indications for endovascular therapy for refractory vasospasm after aneurysmal subarachnoid hemorrhage: experience at the University of Cincinnati. *Surg Neurol* 2002;**58**:131—8.
35. **Cross DT III,** Moran CJ, Angtuaco EE, *et al*. Intracranial pressure monitoring during intra-arterial papaverine infusion for cerebral vasospasm. *AJNR Am J Neuroradiol* 1998;**19**:1319—23.
36. **Rosenberg N,** Lazzaro MA, Lopes DK, *et al*. High-dose intra-arterial nicardipine results in hypotension following vasospasm treatment in subarachnoid hemorrhage. *Neurocrit Care* 2011;**15**:400—4.
37. **Santillan A,** Knopman J, Zink W, *et al*. Transluminal balloon angioplasty for symptomatic distal vasospasm refractory to medical therapy in patients with aneurismal subarachnoid hemorrhage. *Neurosurgery* 2011;**69**:95—102.
38. **Newell DW,** Eskridge JM, Aaslid R. Current indications and results of cerebral angioplasty. *Acta Neurochir Suppl* 2001;**77**:181—3.
39. **Higashida RT,** Halbach VV, Cahan LD, *et al*. Transluminal angioplasty for treatment of intracranial arterial vasospasm. *J Neurosurg* 1989;**71**:648—53.
40. **Hoh BL,** Ogilvy CS. Endovascular treatment of cerebral vasospasm: transluminal balloon angioplasty, intra-arterial papaverine, and intra-arterial nicardipine. *Neurosurg Clin N Am* 2005;**16**:501—16.
41. **Merchant A,** Drazin D, Dalfino J, *et al*. Delayed stenosis as a consequence of angioplasty for subarachnoid hemorrhage-induced vasospasm. Case report. *Neurosurg Focus* 2009;**26**:E23.
42. **Smith WS,** Dowd CF, Johnston C, *et al*. Neurotoxicity of intra-arterial papaverine preserved with chlorobutanol used for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke* 2004;**35**:2518—22.
43. **Mathis JM,** Jensen ME, Dion JE. Technical considerations on intra-arterial papaverine hydrochloride for cerebral vasospasm. *Neuroradiology* 1997;**39**:90—8.
44. **Fraicelli AT,** Cholley BP, Losser MR, *et al*. Milrinone for the treatment of cerebral vasospasm after aneurismal subarachnoid hemorrhage. *Stroke* 2008;**39**:893—8.
45. **Albanese E,** Russo A, Quiroga M, *et al*. Ultra-high dose intra-arterial infusion of verapamil through an indwelling microcatheter for medically refractory severe vasospasm: initial experience. *J Neurosurg* 2010;**113**:913—22.
46. **Avitsian R,** Fiorella D, Soliman MM, *et al*. Anesthetic considerations of selective intra-arterial nicardipine injection for intracranial vasospasm: a case series. *J Neurosurg Anesthesiol* 2007;**19**:125—9.
47. **Tejada JG,** Taylor RA, Ugurel MS, *et al*. Safety and feasibility of intra-arterial nicardipine for the treatment of subarachnoid hemorrhage-associated vasospasm: initial clinical experience with high-dose infusions. *AJNR Am J Neuroradiol* 2007;**28**:844—8.
48. **Platz J,** Berkefeld J, Guresir E, *et al*. Interim Analysis of a Prospective Randomized Trial to Investigate the Efficacy of Endovascular Treatment in Cerebral Vasospasm after Subarachnoid Hemorrhage. *11th Annual International Conference on Neurovascular Events after Subarachnoid Hemorrhage;* July 21 — 23, 2011, Cincinnati, Ohio (abstract).
49. **Fujii Y,** Takahashi A, Yoshimoto T. Effect of balloon angioplasty on high grade symptomatic vasospasm after subarachnoid hemorrhage. *Neurosurg Rev* 1995;**18**:7—13.
50. **Murayama Y,** Song JK, Uda K, *et al*. Combined endovascular treatment for both intracranial aneurysm and symptomatic vasospasm. *AJNR Am J Neuroradiol* 2003;**24**:133—9.
51. **Polin RS,** Coenen VA, Apperson Hansen C, *et al*. Efficacy of transluminal angioplasty for the management of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2000;**92**:284—90.
52. **Elliott JP,** Newell DW, Lam DJ, *et al*. Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 1998;**88**:277—84.
53. **Firlik KS,** Kaufmann AM, Firlik AD, *et al*. Intra-arterial papaverine for the treatment of cerebral vasospasm following aneurismal subarachnoid hemorrhage. *Surg Neurol* 1999;**51**:66—74.
54. **Newell DW,** Eskridge JM, Mayberg MR, *et al*. Angioplasty for the treatment of symptomatic vasospasm following subarachnoid hemorrhage. *J Neurosurg* 1989;**71**:654—60.
55. **Bejjani GK,** Bank WO, Olan WJ, *et al*. The efficacy and safety of angioplasty for cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery* 1998;**42**:979—87.
56. **Coyne TJ,** Montanera WJ, Macdonald RL, *et al*. Percutaneous transluminal angioplasty for cerebral vasospasm after subarachnoid hemorrhage. *Can J Surg* 1994;**37**:391—6.
57. **Clouston JE,** Numaguchi Y, Zoarski GH, *et al*. Intraarterial papaverine infusion for cerebral vasospasm after subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 1995;**16**:27—38.
58. **Kaku Y,** Yonekawa Y, Tsukahara T, *et al*. Super selective intra-arterial infusion of papaverine for the treatment of cerebral vasospasm after subarachnoid hemorrhage. *J Neurosurg* 1992;**77**:842—7.
59. **Kassell NF,** Helm G, Simmons N, *et al*. Treatment of cerebral vasospasm with intra-arterial papaverine. *J Neurosurg* 1992;**77**:848—52.
60. **Firlik AD,** Kaufmann AM, Jungreis CA, *et al*. Effect of transluminal angioplasty on cerebral blood flow in the management of symptomatic vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 1997;**86**:830—9.
61. **Polin RS,** Hansen CA, German P, *et al*. Intra-arterially administered papaverine for the treatment of symptomatic cerebral vasospasm. *Neurosurgery* 1998;**42**:1256—64.
62. **Arakawa Y,** Kikuta K, Hojo M, *et al*. Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: report of seven cases. *Neurosurgery* 2001;**48**:723—30.
63. **Biondi A,** Ricciardi G, Puybasset L. Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurismal subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 2004;**25**:1067—76.
64. **Sehy JV,** Holloway WE, Lin SP, *et al*. Improvement in angiographic cerebral vasospasm after intra-arterial verapamil administration. *AJNR Am J Neuroradiol* 2010;**31**:1923—8.
65. **Badjatia N,** Topcuoglu MA, Pryor JC, *et al*. Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. *AJNR Am J Neuroradiol* 2004;**25**:819—26.
66. **Vergouwen MDI,** Vermeulen M, Gijn JV, *et al*. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: Proposal of a multidisciplinary research group. *Stroke* 2010;**41**:2391—5.
67. **Macdonald RL,** Higashida RT, Keller E, *et al*. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid hemorrhage undergoing clipping: a randomized, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol* 2011;**10**:618—25.
68. **Coenen VA,** Apperson Hansen C, Kassell NF, *et al*. Endovascular treatment for symptomatic cerebral vasospasm after subarachnoid hemorrhage: transluminal balloon angioplasty compared with intraarterial papaverine. *Neurosurg Focus* 1998;**5**:E6.
69. **Oskouian RJ,** Martin NA, Lee JH, *et al*. Multimodal quantitation of the effects of endovascular therapy for vasospasm on cerebral blood flow, transcranial Doppler ultrasonic velocities, and cerebral artery diameters. *Neurosurgery* 2002;**51**:30—43.
70. **Rabinstein AA,** Friedman JA, Nichols DA, *et al*. Predictors of outcome after endovascular treatment of cerebral vasospasm. *AJNR Am J Neuroradiol* 2004;**25**:1778—82.
71. **Terada T,** Kinoshita Y, Yokote H, *et al*. The effect of endovascular therapy for cerebral artery spasm, its limitaions and pitfalls. *Acta Neurochirurg* 1997;**139**:227—34.

# Invasive interventional management of post-hemorrhagic cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage

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**Notes**