Vasospasm after aneurysmal subarachnoid hemorrhage: recent advances in endovascular management
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Introduction
The initial mortality rate of aneurysmal subarachnoid hemorrhage (aSAH) is very high (30–70%) and survivors face a significant risk of morbidity and mortality due to secondary effects especially delayed ischemia due to vasospasm, which is the second leading cause of death and disability in patients with aSAH [1,2,3]. Twenty-five to 30% of the patients who survive SAH from a ruptured intracranial aneurysm suffer from ischemic complications in the ensuing weeks, and 10–15% of patients with SAH die or experience permanent disability due to their ischemic deficits [4–5]. This delayed, reversible narrowing of the cerebral vessels is thought to clinically occur 3–14 days after the hemorrhagic event [1,6].

The exact pathophysiology of cerebral vasospasm still remains largely unknown. Histologically, there are structural alterations in endothelial and smooth muscle cells in the arterial wall [7]. The presence of oxyhemoglobin in the subarachnoid space appears to be necessary to produce these changes [8,9]. The specific mechanisms leading to vasoconstriction, however, are unknown. In vitro, oxyhemoglobin stimulates the secretion of endothelin (ET)-1, a vasoconstrictor, inhibits the vasodilator nitric oxide and produces activated oxygen species [10,11]. These free radicals are believed to play a role in cell membrane lipid peroxidation, possibly mediating the structural changes in the vessel wall.

The ability to predict patients who are likely to suffer the deleterious effects of cerebral vasospasm (CVS) is difficult at best. Several factors such as Hunt and Hess grade, Fischer grade on computed tomography (CT), advanced age [12], race (higher incidence of CVS in Japanese studies) [13], and use of antifibrinolytic agents [14–16] have been shown to be predictors for the occurrence of vasospasm. The mortality rate of CVS is approximately 7% with another 7% of individuals suffering devastating neurological deficits. Although up to 70% of patients have
been shown to have angiographic evidence of CVS, only 20–30% actually present with clinical changes that include both mental status changes and neurological deficits that necessitate acute management [1,6,17–20].

Treatment of cerebral vasospasm
The main treatment of CVS is systemic, and endovascular treatment (EVT) is reserved for vasospasm refractory to habitual medical systemic therapy. In most institutions, placing a central venous catheter and administration of nimodipine, sometimes in addition to hypervolemia or triple-H therapy, is routine [6,20–22]. Endovascular treatments include intratracheal vasodilators and transluminal balloon angioplasty (TBA).

Endovascular treatment of cerebral vasospasm
Endovascular treatment of CVS including intrarterial vasodilators and TBA is widely spreading and it appears to improve neurological outcomes without introducing the patient at significant risk of complications that can accompany prolonged triple-H therapy. Furthermore, with increasing experience in the use of balloons in other intracranial EVT's, interventional neuroradiologists are gaining confidence in their use in cases of CVS.

Indications for endovascular treatment of cerebral vasospasm
For symptomatic CVS, the timing to initiate the treatment appears crucial. Better outcomes were noted in studies initiating the TBA soon after the clinical onset of symptoms. This also may apply to the EVT by intratracheal dilators. The EVT is most often a combination of intratracheal dilators with TBA. The latter is often used in cases of proximal vessel narrowing and/or its persistence despite intratracheal dilator therapy. Non symptomatic CVS can typically be detected at the time of aneurysmal coiling, and prophylactic treatment with intratracheal dilators or TBA maybe of some value. Asymmetric CVS can also be detected during the routine follow-up by transcranial Doppler (TCD). Perhaps in the future when additional confirmatory studies are performed, some Doppler criteria could be established to define parameters whereby prophylactic intratracheal or TBA EVT of CVS would be indicated. There have been some reports in which measures of follow-up of plasma S100B protein levels have been advocated as a potential marker for potentially analyzing neuronal damage related to vasospasm and subarachnoid hemorrhage [23].

Intrarterial vasodilators
In the past few years, new intrarterial dilators have been examined for use in CVS. As a result, papaverine is now considered to be of limited value with far more intrarterial usage of the newer vasodilators.

Papaverine
The most widely studied intrarterial vasodilator, papaverine, is an opium alkaloid. It causes vasodilatation in an as yet incompletely understood mechanism, although it is thought to alter adenosine 39,59-cyclic monophosphate levels in smooth muscle cells [24–28]. It has a half-life of approximately 2 h.

Papaverine should not be mixed with contrast agents or heparin because it may cause precipitation of crystals [29]. Highly concentrated papaverine may have fewer vasodilatory effects and a higher risk of temporary deterioration [30].

Intrarterial papaverine (IAP) administration clearly results in transient reversal of cerebral hypoperfusion with improvement in blood flow velocities measured using TCD ultrasonography and cerebral blood flow (CBF) studies after treatment [29,31–33].

Along with its transient effect requiring multiple treatments [25], the use of papaverine proved to have other limitations, including some adverse effects. The most serious deleterious effects are an increase in intracranial pressure (ICP) [25,33–36], worsening of vasospasm, gray matter injury with neurological deterioration [37], brain stem depression (attention must be made for its use in the posterior circulation), seizures, monocular blindness secondary to crystal emboli formation and transient focal neurological deficits [38].

Another interesting parameter of the action of papaverine on brain tissue was studied in a recent case series [39]. IAP was found to decrease brain oxygen tension (BtO2) in a study of five patients. There was a significant BtO2 decrease in all patients during IAP to a mean of 22.96 ± 2.9 mmHg (P < 0.05), just above the threshold for the normal limits of brain tissue oxygen. BtO2 returned to baseline within 10 min after IAP was suspended. The authors concluded that IAP-induced reduction in BtO2 may help explain why IAP does not improve patient outcome, although it reverses arterial narrowing. This study further supported the undesirable and limited effects of papaverine in the treatment of CVS and has rendered this agent virtually obsolete in the management of CVS.

Nimodipine
Nimodipine is a dihydropyridine agent thought to inhibit voltage-gated calcium channels in the arterial wall smooth muscle cells and results in vasodilation with much
longer half-life than papaverine (9 h). It may also have some direct neuroprotective properties [40–42].

In a very recent study of 26 patients treated by intrartrial nimodipine (IAN) over a total of 42 sessions [43], IAN failed to induce any effect on CVS in eight patients (30.7%). In the remaining 18 patients treated over 22 sessions, IAN was the initial treatment in 14 patients, whereas TBA was given before IAN in four patients. After two bolus injections of IAN of 0.8 mg each, no angiographic changes were observed in three patients, who subsequently received additional intrartrial as a continuous infusion of nimodipine of 4 mg/h for 2 h. Six patients experienced a mean arterial pressure (MAP) decrease of 20 mmHg systolic after the initial bolus. This adverse effect was temporary and was treated easily and quickly with an increase in the vasoactive medication. One patient died 1 day after IAN due to progressive intracranial hypertension. Ischemic lesions following IAN that appeared to be related to CVS were documented in 11 (61.1%) patients. Nine ischemic lesions were classified as minor lesions, whereas two were identified as major infarction on CT. Seven (38.9%) patients developed no additional cerebral minor or major infarction. At the time of discharge, the clinical condition of 11 patients was classified as good (mRS 0–2), one patient had a moderate status (mRS 3–4) and six patients had a poor outcome (mRS 5–6).

**Milrinone**

Milrinone belongs to the phosphodiesterase III inhibitors that combine vasodilating and inotropic properties, resulting from the increase in cAMP in the cytosol of vascular smooth muscle cells and cardiomyocytes. It is widely used to treat patients with acute heart failure.

In a recent study [44] of the combined intrartrial and i.v. use of milrinone in 22 patients, 72 vasospastic territories were treated, requiring a total of 34 selective infusion of intrartrial milrinone (IA-Mil). The infusion resulted in a 53 ± 37% overall increase in vessel diameter. There was a greater vessel diameter increase after milrinone when vasospasm was ‘severe’ with respect to ‘moderate’: 73 ± 23 versus 40 ± 46%, respectively. Milrinone infusion resulted in increased heart rate (HR), but SBP and DBP did not change significantly. Four patients received norepinephrine infusion to maintain MAP (two patients during intrartrial administration and two patients during i.v. infusion). Five patients (23%) had angiographically proven CVS recurrence, which occurred within 48 h after the procedure. Two CVS recurrences were successfully reversed after another IA-Mil infusion. The remaining three patients underwent mechanical angioplasty. Mortality was only 9% and patients who survived had very mild disability scores at 1 year after aSAH. IA-Mil was infused (8 mg over 30 min) in the main artery dedicated to the vasospastic territory. Infusion was repeated once in the same territory if an incomplete reversal was observed. IA-Mil infusion could be repeated in a different territory in situation of extensive vasospasm, with a maximum IA-Mil dose of 24 mg. Intravenous milrinone (IV-Mil) injection is then started and, if well tolerated, the dose was progressively incremented from 0.5 to 1.5 µg/kg per min. This dose incrimination was stopped when tachycardia (HR >100 beats/min) or MAP reduction (>20%) occurred. IV-Mil infusion was maintained during the entire ‘high-risk’ period, that is, up to day 14 after the initial bleeding.

There are several interesting points regarding this study. The technical details are very well described with emphasis on parameters and signs to monitor. It showed that IA-Mil even gives better results with severe vasospasm. Some of the patients with recurrent CVS can respond very well to another intrartrial infusion. Another very important point is the very mild disability scores at follow-up for surviving patients after Milrinone treatment.

**Nicardipine**

Nicardipine has been one of the most widely investigated intrartrial vasodilators in recent years. Nicardipine, a dihydropyridine calcium channel blocker, conveys a greater selective arterial dilatory effect on vascular smooth muscle than in the cardiac muscle. The therapeutic effect is believed to be related to the selective inhibition of transmembrane calcium ion influx into vascular smooth muscle, resulting in a reduction of free calcium ions in these cells and disruption of actin–myosin interaction essential to muscle contraction [45].

Although complications such as prolonged hypotension, pulmonary edema and renal dysfunction have been reported after intravenous (i.v.) delivery of nicardipine, these were not reported with intraarterial nicardipine (IA-Nica) [42].

Recently, IA-Nica was studied during 46 treatment sessions in 22 consecutive patients [46]. Eight patients had additional angioplasty. The average IA-Nica dose was 12 ± 10 mg (range 2–25 mg). The mean decrease in systolic, diastolic and mean blood pressures was 17.4 ± 18.3, 7.7 ± 10.4 and 10.9 ± 11.6 mmHg, respectively. Both the effects on blood pressure and HR were reversible. There was no change in ICP. Measurement of 49 vessels in the 14 patients treated with IA-Nica alone showed a significant increase in arterial diameters (range 1–74%; P < 0.0001). At the time of discharge, 11 patients (50%) were functionally independent (modified rankin scale score 0–2).
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Very recently, IA-Nica treatment was evaluated by CT angiography (CTA) and CT perfusion in six patients [47**]. In five of the six patients, both cerebral blood flow (CBF) and mean transit time (MTT) were improved significantly in affected regions in response to IA-Nica therapy (mean increase in CBF, 41 ± 43%; range –9 to –162%, \( P = .0004 \); mean decrease in MTT, 26 ± 24%; range 0–70%, \( P = .0002 \)). In one patient, the authors were unable to quantify improvement in flow parameters due to section-selection differences between the pretreatment and posttreatment examinations.

The effect of Nicardipine on cerebral blood flow has not been studied before. The current study documents the high positive effect of nicardipine on CBF.

IA-Nica has been also evaluated in conjunction with intrarterial-magnesium therapy. Hypomagnesemia on admission occurs in 38% of individuals with SAH [48]. The use of Mg\(^{2+}\) in SAH comes from its biochemical properties as a physiological antagonist of calcium, which is an important mediator of cerebral vasospasm and is thought to be the most important second messenger in the regulation of smooth muscle contraction. The outcome of the use of magnesium sulfate is controversial. Some studies showed no benefit of its use [49,50], whereas others have proven its efficacy [51,52]. The only common result in all studies is its safety.

IA-Nica was combined to intrarterial infusion of magnesium sulfate in a total of 58 vessels treated in 14 patients [53*]. The treatment was either IA-Nica and magnesium sulfate alone or in conjunction with primary TBA. Forty vessels (69%) had immediate angiographic improvement with IA-Nica and magnesium sulfate alone and 18 (31%) required concomitant TBA with complete reversal of the CVS. Retreatment was required in 13 vessels (22%) and the median time for retreatment was 2 days (range 1–13 days). IA-Nica treatment resulted in the reduction in MAP (12.3 mmHg, SE 1.34, \( P < 0.0001 \)) without any significant change in ICP. Magnesium sulfate infusion was not associated with change in MAP or ICP. Among 31 procedures, immediate neurological improvement was observed in 22 (71%). In 12 (86%) patients, there were no infarctions in the follow-up CT scan acquired between 24 and 48 h. The authors stated that no statistical significant difference was observed in angiographic and clinical outcome of patients treated with the combination therapy in comparison with historical controls treated with IA-Nica alone.

**Verapamil**

Verapamil is a phenylalkylamine calcium channel blocker that inhibits voltage-gated calcium channels in the arterial wall smooth muscle cells and results in vasodilation. The half-life is approximately 7 h. Verapamil was used by Feng et al. [54] in 29 patients who underwent 34 procedures; 52% were treated with intrarterial verapamil (IA-Verap) alone, and this resulted in 44% experiencing increased vessel diameters and 33% exhibiting neurological improvement without complication or ICP issues.

In a recent study [55], IA-Verap showed amelioration of the vasospasm in 10 out of 12 procedures for the treatment of CVS. No statistically significant changes in MAP, HR or ICP were observed after administration of more than 20 mg of IA-Verap and the degree of improvement in CVS was statistically significant based on the author’s grading system. No correlation was found between the change in hemodynamic parameters and the total dose of IA-Verap. In this study, very high doses of IA-Verap were used and these were shown to be well tolerated with no dosage-related adverse significant reactions.

**Fasudil**

Fasudil has numerous mechanisms of action [56–57]. In a study in which 24 territories were treated [56], angiographic improvement was noted in 16 vessels (66.7%). Nine (90%) of 10 patients demonstrated angiographic improvement of CVS. In two (66.7%) of the three who presented with clinical CVS, the neurological symptoms resolved without sequelae. No adverse effects were noted in this study. In another recent study [57] of 23 patients with symptomatic CVS treated over 34 procedures with intrarterial fasudil, 15 showed immediate neurological improvement after the treatment. Angiographic improvement was noted in all patients. However, a significant decrease in MAP from 139.0 ± 3.4 to 126.8 ± 3.6 mmHg \( (P < 0.0001) \) was reported. The authors also observed a disturbance in consciousness that developed in two (8.7%) of the 23 patients, which resolved within 1 h. Although the angiographic and neurological outcome is satisfactory, these adverse effects may hinder the use of fasudil but more investigations about the efficacy of this treatment is needed.

Several intrarterial vasodilators are available for the treatment of CVS, but it is not possible to compare their efficacy and safety as series in the literature are very heterogeneous.

**Transluminal balloon angioplasty**

This technique was initially described by Dotter and Judkins [58] in 1964 for the treatment of peripheral arteriosclerotic obstruction, and has been applied since. In 1984, Zubkov et al. [59] reported the first use of TBA for CVS after aSAH. Since then, investigators have demonstrated the safety and efficacy of this treatment.
modality in numerous case series. The full mechanism of this treatment is not definitely understood. It includes disruption or dysfunction of smooth muscle cells, extracellular matrix or connections between the basement membranes of the cells [24,60].

A limitation of this treatment is that it is only applicable for proximal large vessels, not distal to the proximal segments of the MCA (M1), ACA (A1) or posterior cerebral artery (P1) (i.e. vessels with diameter ≥2 mm). Another major limitation is that it depends on the expertise of the endovascular operator.

Hoh and Ogilvy [25] reported an overall clinical improvement in 62% of patients treated with TBA. Jestaedt et al. [61] have shown that TBA-treated vascular territories had a lower rate (7%) of infarction compared with territories not treated with TBA (38%).

Improvement in angiographic vasospasm is frequently observed after angioplasty [32]. A 100% angiographic improvement was observed in some studies [32,62]. Improvements in CBF after balloon angioplasty have ranged from 60 to 100% [29,31,32,63,64].

Safety and technical efficacy of over-the-wire balloons for TBA was evaluated recently [65]. Thromboembolic complications were noted in 4.7% of TBA treatments in 85 procedures treating CVS in 75 patients. Neither vessel rupture nor perforation is noted in this series. In two recent case reports, delayed stenosis as a complication of TBA was reported [66,67]. Many mechanisms were proposed, including the disruption of extracellular matrix [68] or activation of reactive oxygen species, the superoxide radical, which exerts numerous effects such as inactivation of endothelium-derived relaxing factor, lipid hydroperoxide–mediated modulation of vascular tone and platelet activation, which can lead to stenosis [69].

It should be outlined that, in our own experience, we have observed in few cases and recurrence of vasospasm after TBA leading to a second TBA in some cases.

An important point is when to start the TBA after the onset of clinical CVS. Moreover, investigators have asked whether prophylactic TBA (pTBA) is of value in high-risk patients or not. Reports recommended starting the TBA in a 2–24 h time window after the onset of clinical CVS [31].

Very recently, the results of a multicentric randomized phase II study for the evaluation of pTBA in patients with Fisher grade III SAH were published [3**]. One hundred and seventy high-risk patients with no clinically evident signs of CVS were randomized and 85 patients underwent pTBA. The study did not demonstrate a significant difference in the primary endpoint (Glasgow Outcome Scale score). The authors concluded that pTBA does not improve the poor outcome of patients with Fisher grade III subarachnoid hemorrhage, but the study did demonstrate a trend toward fewer patients developing vasospasm or needing therapeutic TBA after pTBA was done (23.5% versus 31.8% in the control group). The procedure-related complication rate of pTBA was 5% (four patients), an approximate risk of 1% per treated vessel segment. This involved arterial perforation by the guide wire in two patients and vessel rupture due to balloon inflation in the other two. Three of the four patients died and the fourth had a good recovery. The procedure showed no benefit and was responsible for three deaths (4%) from vessel rupture, an incidence rate higher than the 1.1% reported in the literature [25].

### Conclusion

The current prophylactic management of CVS after aSAH (i.v. nimodipine and hypervoleimia) is still valid. The role of endovascular therapy occupies an important place in the treatment of CVS. It is indicated in cases in which symptomatic CVS occurs regardless, or in persistence to, medical prophylactic management. Two modalities have been demonstrated to show primary efficacy of vessel diameter enlargement: intrarterial vasodilators and TBA. Intrarterial vasodilators, such as papaverine, is now no longer used due to its numerous adverse effects and its transient action. Several intrarterial vasodilators are efficient against CVS, including nimodipine, nicardipine, milrinone, verapamil and fasudil. No direct comparison of their efficacy is available. TBA is the most efficient modality for the treatment of CVS, although it has not be demonstrated in a prospective randomized series. It is operator dependent, but with the widespread and growing experience of operators using balloons in other treatments, like the balloon remodeling technique in coiling procedures, the risk of this technique is becoming minimal. Some case series suggest highly favorable results and less CVS recurrence. Finally, treatment of CVS is a combined approach, by the prophylactic measures, the intrarterial vasodilators and the TBA in advanced cases.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This study illustrates the nonfeasibility of prophylactic TBA in CVS on patients outcome.


This study points to the relation between hypomagnesaemia and CVS. Efficacy of magnesium sulfate on CVS is contradictory in the literature but its use is well tolerated.
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