

# Endovascular treatment of cerebral vasospasm following aneurysmal subarachnoid hemorrhage

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## Summary

Endovascular treatment by balloon angioplasty or intra-arterial papaverine infusion has been established as a valuable treatment option in patients with cerebral vasospasm refractory to maximal medical therapy. A summary of the indications, applications and limitations is provided for microcatheter guided selective papaverine infusion and transluminal balloon angioplasty in patients who sustain cerebral vasospasm following subarachnoid haemorrhage. Structured neuro-intensive and endovascular treatment of imminent vasospasm integrate papaverine administration and balloon angioplasty as complimentary rather than alternative techniques.

*Keywords:* Transluminal balloon angioplasty; microcatheter guided papaverine infusion; endovascular treatment; cerebral vasospasm; subarachnoid haemorrhage.

## Introduction

Cerebral vasospasm remains a leading cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage [9]. Preventive measures include surgical, medical and endovascular treatment. Surgical measures are performed in conjunction with clipping of the aneurysm and consist of flushing of the subarachnoid space and opening of the lamina terminalis. In case of endovascular treatment of the ruptured aneurysm, angiographic vasospasm may be treated within the same session following occlusion of the aneurysm. Endovascular means therefore are only rarely preventive but are usually aimed at targeted treatment of symptomatic and/or angiographic vasospasm. Medical preventive treatment is always instituted consisting of calcium antagonist therapy in a first step and hypertensive, hypervolemic therapy and hemodilution (triple H therapy) when rising flow velocities in basal cerebral arteries indicate impeding vasospasm.

The discrepancy between a high incidence of angiographic vasospasm or high flow velocity recordings by transcranial colour Doppler sonography (TCD) between day 7 and 15 and a significantly lower incidence of symptomatic vasospasm is explained by several factors. The high sensitivity of angiography and TCD to detect and localize vasospasm, the individuals potential to compensate vasospasm by way of collaterals, and last but not least the ability to judge a patients clinical condition and its deterioration depending on the Hunt and Hess grade.

## Indication and methods

Cerebral vasospasm that is refractory to maximal medical management is an indication for endovascular therapy. In patients being well amenable to clinical assessment progressive vasospasm is indicated by confusion, deterioration in the level of consciousness and/or development of a new focal neurologic deficit. In patients with Hunt and Hess grade IV and V and in patients being intubated and ventilated recognition of vasospasm is dependent on indirect means only. Several techniques (bulbus oximetry, internal jugular vein lactic acid differences) have been investigated to substantiate the presence and location of cerebral vasospasm. TCD recordings have proven to be efficient and sensitive but not specific for cerebral vasospasm. TCD performed on a regular basis provides support to non-invasive recognition of vasospasm when time averaged maximal flow velocities exceed 140–160 cm/s within the anterior, or middle cerebral artery and intracranial internal carotid artery. A sudden rise of 50 cm/s is indicative of moderate to severe vasospasm as well. Prior to the decision to perform endovascular treatment a cranial CT is performed. The objective is to exclude hydrocephalus, haemorrhage, infarction or infection as causes of clinical deterioration or rising intracranial pressure values.

A new technique that is progressively being integrated into the diagnostic regimen is perfusion CT. Cerebral infarction either evident on noncontrast CT or on blood volume parameter maps is a contraindication to perform endovascular therapy. However, significant differences in territorial or hemispheric transit times not only substantiate the need to perform endovascular therapy but may help to direct treatment to the vascular territory most severely affected.

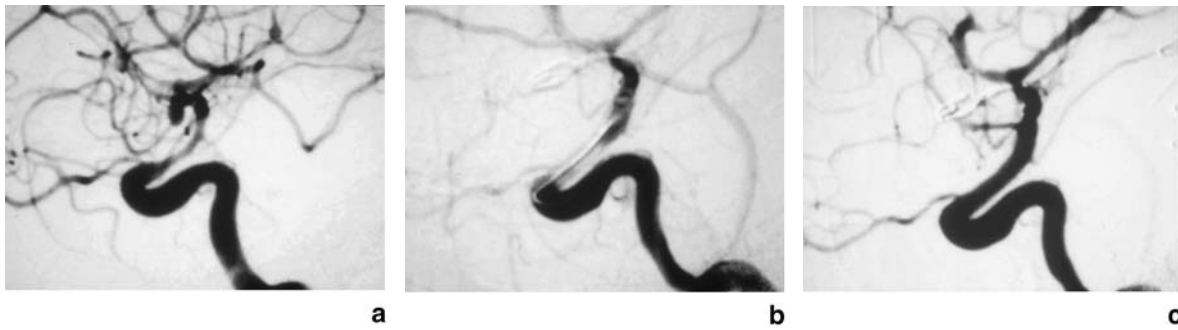


Fig. 1. 58 year old female with ruptured middle cerebral artery bifurcation aneurysm. Progressive right sided hemiparesis on day 8 following subarachnoid haemorrhage. The lateral projection of the left carotid angiography (a) reveals marked vasospasm of the supraclinoid internal carotid artery. Transluminal balloon angioplasty (b) due to circumscribed proximal location of vasospasm. Left lateral projection of carotid angiography following angioplasty (c) depicts elimination of vasospasm with restoration of normal vessel calibre

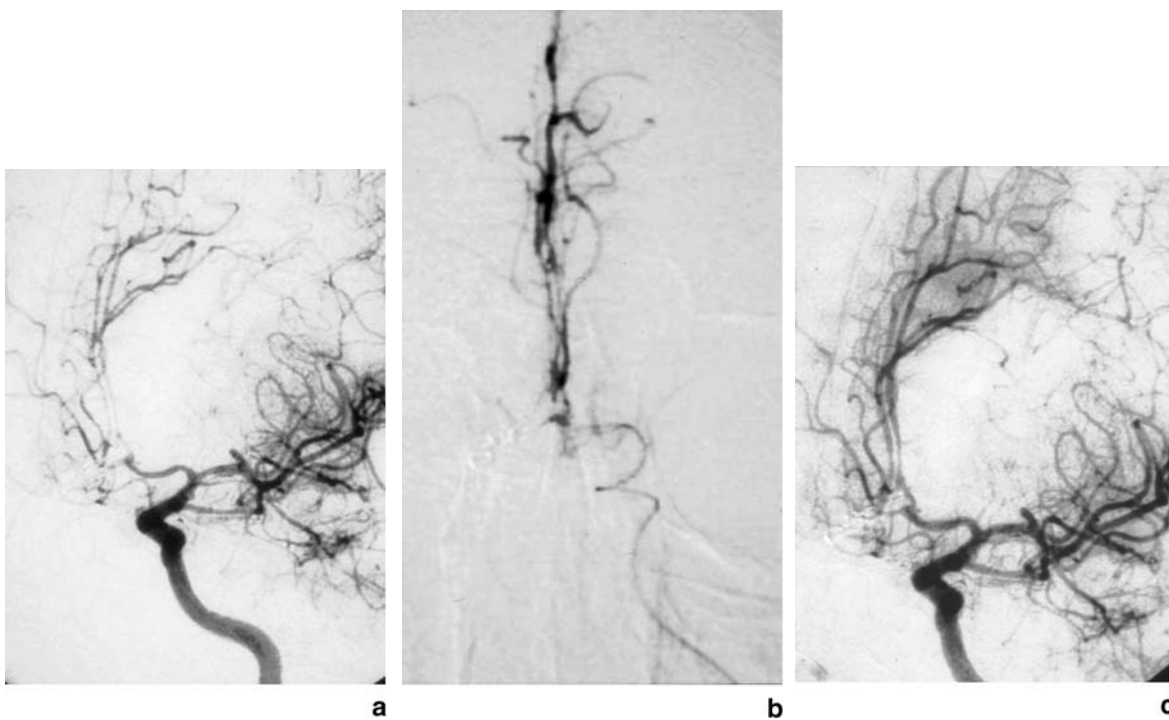


Fig. 2. 65 year old male with ruptured Acom aneurysm. Confusion, right leg paresis on day 11 following subarachnoid haemorrhage. The antero-oblique projection of the left carotid angiography (a) demonstrates marked vasospasm of both pericallosal arteries which are supplied via a moderately narrowed left A1 segment. The A1 on the right side was hypoplastic. Ap projection after contrast injection via the selectively positioned microcatheter with the tip within the distal left A1 segment (b). Antero-oblique projection of left carotid angiography following administration of 300 mg papaverine (c) shows marked vasodilatation within both A2 segments. The anterior cerebral artery and the proximal middle cerebral artery have increased in calibre as well

The presence, location and degree of vasospasm are confirmed by digital subtraction angiography (DSA). DSA as an invasive diagnostic procedure is performed only with the intent to perform endovascular treatment.

### Endovascular treatment

The objective of endovascular treatment of cerebral arterial vasospasm is to restore adequate blood flow

and to prevent cerebral ischemia and infarction. Cerebral arterial vasospasm consists of an active and passive component. The active constituent is caused by actin-myosin cross linking, while the passive component is due to a fixed contractile apparatus within the tunica media of the vessel wall. Endovascular treatment is aimed at reversal of both components. Two different techniques are applied: mechanical or phar-

macological vessel dilatation. Mechanical vasodilatation is achieved by means of transluminal balloon angioplasty and is directed towards a circumscribed proximal vessel segment. Balloon angioplasty was first introduced in 1984 in the setting of clinical vasospasm [18]. Balloon angioplasty reverses both active and passive components of vasospasm.

Pharmacological endovascular dilatation is based on continuous intraarterial infusion of papaverine via a microcatheter positioned within the proximal intracranial vessel territory affected by vasospasm. Papaverine treatment is effective within the entire vessel territory primarily treated and recirculation exerts an effect within other vascular territories as well. Its action is predominantly directed towards the active component of arterial vasospasm.

Treatment by balloon angioplasty is targeted to proximal intracranial arterial vasospasm. Proximal vasospasm affects the supraclinoid internal carotid artery, the middle cerebral artery mainstem, the proximal middle cerebral artery branches (M 2 segments) and the A1 segment of the anterior cerebral artery [3, 16]. The arteries of the vertebro-basilar system including the proximal posterior cerebral arteries (P1) are accessible to balloon angioplasty as well, but only rarely exhibit vasospasm. Vasospasm occurring distal to the aforementioned vessel segments is not accessible to endovascular balloon treatment due to small vessel size. Balloon angioplasty is performed with compliant balloon systems with a diameter of 1.5 and 2.0 to 3.0 mm. Even though angioplasty is directed to and effective on a morphological basis in circumscribed proximal vessel segments only, the rationale is to improve blood flow, oxygenation and metabolism within the distal arterial territory as well [1, 5].

In order to achieve sufficient dilatation within a longer proximal vessel segment or in multiple vessels, repeated balloon inflations may be required in different positions. In patients with maximum degree proximal vasospasm pre-treatment with intraarterial papaverine injection is at times the only means to achieve sufficient predilatation to allow a balloon to be placed without obstructing blood flow. Additional balloon angioplasty on the other hand remains an option in patients with proximal vasospasm refractory to papaverine treatment [11].

Balloon angioplasty mechanically reverses the active and passive component of vasospasm. By distension of the internal elastic lamina and tunica media, smooth muscle constriction and fixation of the con-

tractile filaments and muscle fibres are thus eliminated. Balloon angioplasty therefore bears the risk of vessel rupture in case of overdilatation of the vessel.

Vasospasm following angioplasty is not prone to recurrence. The dilating effect of transluminal balloon angioplasty was found to persist in 99% [3] and 100% [16] of vessel segments treated.

Limitations of balloon angioplasty include the segmental nature of dilatation and the inaccessibility of distal vessel segments. A contraindication to balloon angioplasty is a vasospastic vessel segment harbouring a clipped or coil treated side wall aneurysm and an unsecured aneurysm at or distal to the vessel segment affected by vasospasm. Manifest cerebral ischemia proven by CT or diffusion MR is a contraindication for any endovascular intervention as well. In patients with symptomatic or severe vasospasm at the time of initial angiography after subarachnoid hemorrhage a combined treatment approach may be performed starting with obliteration of the aneurysm followed by initiation of spasmolytic therapy. In 12 patients with severe vasospasm on admission combined GDC occlusion of the aneurysm and balloon angioplasty was performed in 6 patients, papaverine infusion in two cases or both treatment modalities in 4 patients in a single session. In all patients angiographic improvement of vasospasm was obtained [12].

Microcatheter guided intraarterial papaverine infusion is an alternative or supplementary treatment to balloon angioplasty in patients affected by vasospasm. First introduced in 1992 Kaku and Yonekawa [7] established superselective application of papaverine via a microcatheter. The authors were the first to report administration of papaverine in conjunction with PTA. Superselective papaverine application via a microcatheter which is placed within the proximal vessel segment has since evolved as a standard technique. Kassell and coworkers [8] established 300 mg papaverine as a standard dose dissolved within 100 ml of saline. Heparine should not be added in order to prevent crystal formation. Infusion is performed over a minimum of 30 minutes. Papaverine may also be administered as an adjunct following proximal angioplasty in order to reverse additional distal vasospasm. The long term effects of intraarterial papaverine treatment as the sole therapy has been questioned in view of its short pharmacologic half life of 8.5 minutes. After papaverine infusion a beneficial effect was found to be limited to the first three hours only by continuous long term thermal diffusion rCBF measurements [17].

Recurrence of vasospasm following papaverine treatment is not uncommon. Repeated infusions due to recurrence of vasospasm have been reported in 23.3% [16] and even in 37.5% of patients [13]. The incidence of a second recurrence following standard dose papaverine treatment is low [6.7%] and tends to affect different vessels than the ones previously treated [16]. In case of multi-territorial vasospasm or recurrence, the papaverine dose may be increased up to 600 mg [13, 16]. Recurrence of vasospasm accounts for the major limitation of papaverine treatment. However, repetitive papaverine administrations may be performed based on symptoms, TCD recordings or angiographic findings. Even though the efficacy of papaverine has been questioned within a later stage of vasospasm, a maintained effect corresponding to initial treatments has been shown. In 17 patients with recurrent vasospasm papaverine administration reversed prolonged circulation time in 90 of 91 (99%) vessels treated. Repeated infusions were as successful as the primary treatment [10]. In case of symptomatic vasospasm treatment should be instituted as early as possible. A two hour window was found to exist for restoration of blood flow by endovascular treatment [15].

Preventive treatment without clinical or angiographic evidence of vasospasm is not indicated in view of the following limitations and side effects. Limitations of papaverine treatment are raised intracranial pressure, and systemic hypotension. Side effects consist of respiratory depression and brainstem dysfunction in vertebral artery infusions [5], systemic hypotension and propensity to seizures in supratentorial arterial infusions [2].

Both papaverine and combined angioplasty and papaverine treatment are conducted under general anaesthesia. Elevated intracranial pressure is strongly associated with poor outcome and death in a series of 62 patients treated by balloon angioplasty and papaverine at the University of Cincinnati [1]. Papaverine was most effective as a single dose treatment in distal monoarterial vasospasm, if balloon angioplasty was impossible or not considered safe. Balloon angioplasty was indicated as an early treatment in multi-territorial proximal vasospasm. In another study the efficacy of balloon angioplasty was assessed in comparison to papaverine therapy and to combined angioplasty and papaverine spasmolytic treatment [14]. While the effect on proximal flow velocities was most pronounced in 12 patients treated with balloon angioplasty, the effect on cerebral blood flow and increase in vessel diameter was

more prominent in 20 patients following papaverine application. Combined treatment by papaverine and angioplasty in 13 patients proved most effective with respect to increase in cerebral blood flow and arterial diameter.

Despite aggressive instantaneous and repetitive treatment attempts by endovascular interventions the overall benefit with respect to patients outcome is difficult to assess. Early clinical improvement following endovascular treatment is strongly associated with favourable outcome [4]. In a review of 38 patients enrolled as part of the American trial of tirilazad the authors state the effectiveness of transluminal balloon angioplasty but conclude that the superiority to medical management is questionable [5]. In a series of 30 patients treated with papaverine infusion and angioplasty permanent clinical improvement was achieved in 73.3% of patients [16]. These results compare favourably with a rate of 69% permanent improvement in a series of 24 patients with papaverine as the sole treatment [13] and are identical to a series of 101 PTA treated vessels with maintained clinical improvement in 74% of patients [3].

## Conclusion

The complexity of vasospasm with respect to mono- or multiterritorial location, proximal or distal vessel territory involvement and different degrees of severity render correlation of angiographic improvement with clinical improvement difficult [5, 16]. This is not surprising in view of the fact that endovascular treatment is only one constituent of the challenging neuro-intensive management of patients after subarachnoid hemorrhage.

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