

Prevention and Treatment of Vasospasm Following Subarachnoid Haemorrhage

Delayed ischaemic neurological deficit (DIND) is a major cause of morbidity and mortality following aneurysmal subarachnoid haemorrhage (SAH). This condition is potentially preventable and treatable. The pathogenesis of the condition is unclear although vasospasm is of paramount importance. The diagnosis of DIND secondary to vasospasm remains contentious and is reliant upon clinical status and cerebral imaging techniques. Therapeutic interventions require high dependency care and are not always effective. In this article the historical recognition of cerebral vasospasm is described, the broad pathophysiological mechanisms that may be involved are outlined and the management options are reviewed.

Introduction

In 1949, the Australian neurologist Edward Graeme Robertson hypothesised that arterial spasm may be responsible for post-subarachnoid haemorrhage (SAH) cerebral infarction.¹ In 1951, Denny-Brown attributed post-SAH deterioration to cerebral vasospasm.² The same year two Americans, Ecker and Riemenschneider, demonstrated angiographic spasm in six patients with aneurysmal SAH.³ In the mid 1960s Stornelli and French reported that angiographic vasospasm indicated a poor prognosis.⁴ Allcock and Drake conducted a thorough angiographic examination of 83 patients before and after treatment of their intracranial aneurysms and found evidence of vasospasm in over 40% of patients.⁵ They reported that patients with vasospasm were more likely to have a poor outcome and concluded that arterial spasm was the main cause of morbidity and mortality in patients with ruptured intracranial aneurysms. The time course of vasospasm was shown by Fischer, who reported that neurological deterioration occurred in one third of SAH patients, and was maximal between days 2 and 4 following the bleed.⁶

In 1970 the normal sizes of the carotid artery and the major cerebral branches were reported enabling objective assessments of vasospasm.⁷ Weir et al. reported that the ratio of intracranial to extracranial vessel diameter was reduced in some subarachnoid patients.⁸ They also demonstrated that this vasospasm was maximal between days 4 to 8 following the initial bleed and had resolved by day 12. In the International Cooperative Study, Kassell et al. showed that the clinical and radiological features of vasospasm were discordant. Delayed ischaemic neurological deficits (DINDs) occurred in 30% of patients whereas angiographic vasospasm was observed in up to 70% of cases.⁹ In addition DINDs were also noted to occur in the absence of angiographic vasospasm in some cases.

Epidemiology

In the UK aneurysmal subarachnoid haemorrhage has an incidence of approximately 8-10 per 100,000 per year, although population-based studies suggest that the incidence may be higher.¹⁰ DINDs are a major cause of morbidity and mortality following subarachnoid haemorrhage.^{11,12} National Audit Data on 2420 SAH patients found no statistically significant difference in the incidence of DINDs between coiled and clipped patients.¹² Even though The International Subarachnoid Aneurysmal Trial (ISAT) provided Grade 1 evidence for improved one year outcome for coiling over clipping of small anterior circulation aneurysms, a recent meta-

analysis found that there was no difference in the incidence of DINDs between coiling and clipping.^{13,14}

Pathophysiology

DINDs may be due to focal or global ischaemia and do not necessarily occur in arterial territories directly related to the site of the aneurysmal rupture. Whether the ischaemia is due to spasm of the large arteries, microvascular insufficiency or some other unelucidated mechanism is uncertain. Most pharmacological research has focused on the role of vasospasm in causing DINDs. It appears that the initial trigger for vasospastic ischaemic deficits is leakage of blood into the subarachnoid space. Fisher et al. noted that vasospasm appears to be associated with the blood load in the subarachnoid space.¹⁵ Oxyhaemoglobin and platelets have been implicated as molecular agents that must be present in the subarachnoid space in order for vasospasm to occur.^{16,17} Various molecular mechanisms have been implicated in the development of DIND downstream of this 'blood-trigger'. These include reduced endothelial synthesis of the vasodilator nitric oxide (NO); reduced vasodilatory action of nitric oxide; and increased release of the vasoconstrictor endothelin-1 (ET-1). The possible imbalance of NO and ET-1 in mediating the protein kinase C dependent contractile system in vessel walls has provided potential new therapeutic strategies by means of NO activators/donors and ET-1 antagonists. In addition free radical generation may be a contributing factor to the pathogenesis of DINDs (Figure 1).¹⁸⁻²⁰

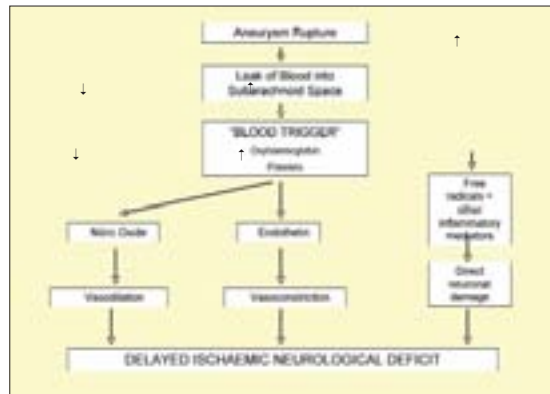


Figure 1. Pathophysiology of vasospasm.

Assessment of a patient with a DIND

Clinical assessment, transcranial Doppler ultrasonography (TCDs), cerebral perfusion imaging and digital subtraction angiography (DSA) are all used in the clinical arena to assess cerebral blood flow parameters in patients with a DIND.

Clinical assessment

Clinical assessment is a robust method of assessing the functional integrity of cerebral tissue and is carried out by careful close monitoring of neurological status. A diagnosis of DIND is made when other possible causes of neurological deterioration such as rebleeding, hydrocephalus, seizures and electrolyte abnormalities have been excluded. Neurological deterioration may include focal deficits such as unilateral limb weakness or dysphasia, or global impairment such as confusion or



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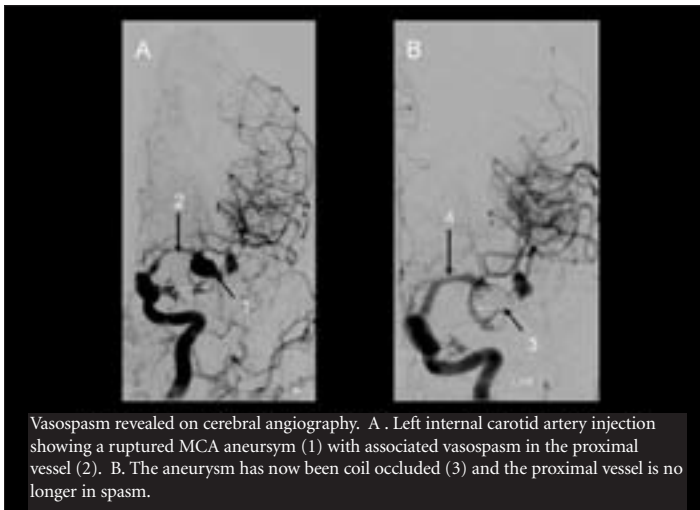


Figure 2. Vasospasm revealed on cerebral angiography.

DIAGNOSIS & MANAGEMENT OF PATIENTS WITH VASOSPASM WITH A SECURED RUPTURED ANEURYSM	
Diagnosis	
1) Clinical evidence of vasospasm	
<ul style="list-style-type: none"> • Focal neurological deficit in the absence of another underlying cause • CT head to exclude rebleed prior to treatment • Exclude electrolyte abnormalities 	
2) Angiographic evidence of vasospasm at the time of coiling procedure or diagnostic angiography	
3) Patients at risk of vasospasm	
<ul style="list-style-type: none"> • High Fisher grade 3 on CT • EEG changes/epilepsy fit • Central cell swelling 	
4) CT perfusion, TCDs, consider cerebral angiography if interventional treatment proposed	
Management	
1) HDU monitoring: arterial line, CVP, 4 hourly ABC, twice-daily US&Mg, daily urine Na ⁺ /hemat, daily TCDs	
2) HHH Therapy	
Hypertension	• BP parameters set according to neurological improvement, may need inotropic support
Hypervolaemia	• CVP 8-10 cmH ₂ O in spontaneously ventilating patients
	• Background crystalloids 120ml/hr • Fluid bolus as required
	• May need to consider hypertonic saline
Haemodilution	• Aim for haematocrit 30-35%
3) Continue prophylactic measures with nimodipine	

Figure 3. Diagnosis and management of patients with vasospasm with a secured ruptured aneurysm.

increased drowsiness. Several risk factors have been identified which independently predict symptomatic vasospasm. These include blood load in the basal cisterns, a Glasgow Coma Scale score of less than 14 at presentation and rupture of anterior cerebral (ACA) or internal carotid (ICA) aneurysms.²¹ Raised troponin levels and the presence of cerebral salt wasting syndrome may also be risk factors for the development of vasospasm.^{22,23}

Transcranial Doppler (TCD) ultrasonography

Blood flow velocity through the cerebral arteries is inversely proportional to arterial diameter. TCD is used to measure flow velocity and thereby indirectly assess the severity of vasospasm.²⁴ However, one of the main conceptual difficulties with TCDs is that flow velocity may be raised due to increased flow (hyperaemia) or arterial narrowing (vasospasm). To help distinguish vasospasm from hyperaemia the Lindegaard ratio of middle cerebral flow velocity to extracranial carotid flow velocity is used. A Lindegaard ratio > 6 represents severe vasospasm.²⁵ Lindegaard et al. also showed that MCA flow velocity > 200 cms⁻¹ was predictive of a 3-fold constriction in the diameter of the artery.²⁵

One of the criticisms of TCDs has been that they do not correlate with cerebral blood flow or perfusion as measured by modalities such as Xenon CT or PET scanning.²⁶ Despite the conceptual limitations of TCDs, there is good evidence to support their clinical application. Vora et al. compared MCA velocities with angiographic studies in 101 patients retrospectively and 44 patients prospectively and found that TCDs had positive predictive values of 87% for velocities >200 cms⁻¹

and negative predictive values of 94% for velocities <120 cms⁻¹.²⁷ One of the interesting findings of Vora et al's study was that the Lindegaard ratio did not alter the predictive value of TCDs. Fontanella et al. undertook a prospective study of 786 patients with anterior circulation aneurysmal SAH where any patient with a MCA velocity of > 120 cms⁻¹ underwent cerebral angiography. They reported that TCDs had a 97% predictive value in middle cerebral artery spasm.²⁸ TCD's have a distinct advantage over angiography in that they are less expensive, non-invasive and can be used at the bedside to monitor response to treatment. Certainly TCD's are user dependent and provide more reliable data if serial measurements are recorded in individual patients.²⁹ TCDs should be viewed as a useful adjunct in the management of DIND patients when used appropriately.

Cerebral perfusion imaging

The numerous modalities available include positron emission tomography (PET), xenon-enhanced computed tomography (Xe-CT), single-photon emission computed tomography, and CT-perfusion techniques. CT-perfusion is less time-consuming and more readily available and therefore appears set to become a widespread tool in the detection of early vasospasm.³⁰ Xe-CT scanning protocols are well described and can provide evidence of cerebrovascular reactivity if used in conjunction with CO₂ provocation testing. PET is not widely available but does help determine not only the cerebral blood flow in a DIND patient but also the oxygen uptake (oxygen extraction fraction) and cerebral metabolic rate (CMRO₂). Such studies assess the degree of coupling between CBF and brain metabolism and may provide an insight into the reasons for the discordance between the prevalence of angiographic vasospasm and DIND. Functional MR imaging is hampered to some extent by the restless nature of many of the patients with DINDs.

Digital Subtraction Angiography (DSA)

The evolution of non-invasive techniques to assess cerebral perfusion has reduced the utilisation of DSA to those cases where an endovascular therapeutic option is being pursued (Figure 2).

Management

Cerebral vasospasm results in altered autoregulation of cerebral blood flow and ultimately reduced cerebral perfusion resulting in ischaemic damage to the brain. Due to the delayed onset of vasospasm, prophylactic strategies may be effective. Therapeutic modalities have evolved that aim to reverse vasospasm and protect potentially ischaemic cerebral tissue (Figure 3).

Hypertensive, Hypervolaemic and Haemodilution (HHH-therapy)

Kosnik and Hunt were the first to report the effects of raising arterial pressure in cerebral vasospasm in 1974.³¹ They reported a series of seven patients in whom the neurological deficit was reversed promptly by the elevation of systemic blood pressure and found that infarction was prevented in some of these patients. Kassell et al. carried out a larger study in 1982 in which hypertensive therapy and intravascular volume expansion in a series of 58 patients permanently reversed neurological deficits in 47 patients and transiently reversed deficits in four patients.³² Since these early studies, HHH-therapy evolved with the inclusion of haemodilution to augment rheological properties of blood flow. Although HHH-therapy has not been examined with a randomised controlled trial, it has become the mainstay of medical therapy for the treatment of vasospasm and more recent investigations using cerebral monitoring support its continued use.³³ There is a lack of consensus as to how HHH-therapy should be achieved although monitoring of clinical condition, CVP measurement, arterial BP measurement and serial TCD measurements in a high-dependency setting are commonly employed. HHH-therapy is associated with significant complications including pulmonary oedema, myocardial ischaemia and electrolyte abnormalities including dilutional hyponatraemia.³⁴ Raab et al. have found that in poor grade subarachnoid patients the use of moderate hypertension, normovolaemia, and haemodilution may improve cerebral oxygenation but with less complications than aggressive hypertensive therapy.³³ The prophylactic use of HHH-therapy has not

been widely supported and preliminary trials have not shown any benefits.^{35,36} Hypotension and hypovolaemia should be avoided in all patients at risk of DIND. In future years functional imaging modalities and invasive cerebral tissue monitoring may lead to refinements in the optimisation of cerebral perfusion augmentation therapy.

Calcium antagonists

Allen et al. reported the first randomised, double-blind, placebo-controlled trial (RCT) of nimodipine.³⁷ They looked at prophylactic use of nimodipine for 21 days following aneurysmal SAH in 125 patients of good grade and found that nimodipine was effective in reducing neurological deficits. Pickard et al. reported the largest RCT in 1989 which included 554 SAH patients.³⁸ Follow-up at 3 months showed that 21 days of nimodipine treatment was effective in reducing the incidence of cerebral infarction by one-third (22% with nimodipine compared to 33% with placebo) and also improved overall clinical outcome. At least five other RCTs of prophylactic nimodipine have been carried out. A meta-analysis concluded that the effectiveness of nimodipine had been well demonstrated and supported routine prophylactic nimodipine administration.³⁹ Although other calcium antagonists such as nicardipine have been investigated a systematic review of 27 RCTs concluded that there was only evidence to support the prophylactic use of nimodipine.^{40,41}

Magnesium sulphate

Magnesium is a cerebral vasodilator and may also have neuroprotective effects by preventing influx of calcium into injured neurons via excitatory amino acid receptor blockade. The preliminary results of the IMASH trial showed that a 14 day infusion of magnesium sulphate may reduce the incidence of symptomatic vasospasm and justifies the continuation of the study to try and establish a clinically useful prophylactic treatment.^{42,43}

Statins

Statins are known to increase the eNOS activity and theoretically, therefore, may reduce vasospasm. Two small randomised studies have demonstrated a reduced incidence of vasospasm in patients treated with simvastatin or pravastatin.^{44,45} In the pravastatin study the incidence of TCD detected vasospasm was reduced by 32% with a reduced incidence of DIND and mortality. At six months beneficial effects on physical and psychological aspects of functioning were reported.⁴⁶ A multicentre randomised controlled trial looking at the potential benefit of simvastatin (40mg for 21 days) in aneurysmal SAH (STASH) is underway.⁴⁷

Erythropoietin

Erythropoietin (EPO) has been found to have neuroprotective effects in the central nervous system.⁴⁸ It is unclear how this effect is exerted although there is evidence to suggest activation of endothelial nitric oxide synthase

(eNOS) occurs.⁴⁹ However, a double-blind randomised trial of EPO versus placebo in 73 patients failed to show any beneficial effect in cerebral vasospasm.⁵⁰

Endothelin-receptor antagonists

There has been much interest in agents which will redress the putative imbalance in the control of PKC-dependent contractile mechanisms in vasospasm. These include NO donors and ET-1 antagonists. The preliminary results of a randomised clinical series treated with the ET-1 antagonist clazosentan appears to show improvements in CBF in patients with established vasospasm.⁵¹ Further work is required in this area.

Pharmacological implants

Aneurysm surgery provides an opportunity to investigate the effects of local pharmacological treatments as prophylaxis against vasospasm. No beneficial effects were reported in the only randomised controlled trial published using a thrombolytic agent.^{52,53} Kasuya et al. reported the effect of placing prolonged-release nicardipine implants in the basal cisterns after aneurysm clipping. Although initial results are promising for the proximal vessels, the effect is less on the more distal cerebral circulation and requires further investigation.^{54,55}

and colforsin daropate carries the theoretical benefit of delivering a high dose of vasodilator directly to the resistance vessels, clinical studies have shown vasodilatation to be transient and without sustained benefit.^{61,62} In addition vasodilatation may cause an elevation of intracranial pressure.⁶³ Such strategies remain experimental.

Conclusion

DINDs following subarachnoid haemorrhage are devastating and are associated with a high morbidity and mortality rate. The delayed-onset of this disorder which appears to be associated with vasospasm and impaired cerebral perfusion continues to stimulate clinicians and neuroscientists to find preventative and therapeutic treatment strategies. There is no consensus regarding the underlying pathology or the optimal methods to diagnose and treat DINDs. Effective management is demanding on resources and involves input from neurosurgical, neuroradiological and neurocritical care specialties. A 'same-hymn-sheet' approach may be required within individual centres in order to establish consistency of investigation and treatment so that new therapeutic modalities can be accurately assessed. Cerebral vasospasm remains a challenge for all clinicians interested in reducing the adverse outcomes associated with subarachnoid haemorrhage.

Clinical vasospasm is a diagnosis of exclusion

Endovascular therapies

Endovascular techniques employed in the therapy of vasospasm include mechanical dilatation of major cerebral arteries using transluminal balloon angioplasty (TBA) and local injection of vasodilator agents. TBA was first reported in 1984 in a series of 33 SAH cases.⁵⁶ Since that time defined criteria to determine the applicability of endovascular techniques have been described.⁵⁷ These include the absence of an established infarct on CT scanning, the persistence of neurological deficits despite medical management (HHH-therapy) and angiographic evidence of vasospasm in a distribution consistent with the neurological deficit.

Two large studies support a role for TBA in the management of vasospasm.^{58,59} In both of these TBA improved angiographic spasm in over 90% of cases and improved clinical status in 30-40% of patients. However the complications of TBA include vessel rupture which has been reported at a rate of 4%.⁶⁰ Since many radiologists consider any beneficial effects of TBA to be short-lived the technique has not been universally adopted. A peer reviewed publication of the Balloon Prophylaxis of Aneurysmal Vasospasm Study is awaited.

Although the intra-arterial injection of vasodilators such as papaverine, nimodipine, nicardipine, verapamil, milrinone, fasudil,

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