British Journal of Anaesthesia **109** (3): 315–29 (2012)
doi:10.1093/bja/aes264

BJA

Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm

M. J. Rowland*, G. Hadjipavlou, M. Kelly, J. Westbrook and K. T. S. Pattinson

Nuffield Division of Anaesthetics and FMRIB Centre, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

* Corresponding author. E-mail: mrowland@fmrib.ox.ac.uk

Editor's key points

- Delayed cerebral ischaemia (DCI) is the major cause of morbidity and mortality after aneurysmal subarachnoid haemorrhage.
- Nimodipine remains the only proven therapeutic intervention.
- Some early advances have been made in understanding the pathophysiology of DCI.
- Better understanding is required to drive therapeutic advances.

Summary. Despite improvements in the clinical management of aneurysmal subarachnoid haemorrhage over the last decade, delayed cerebral ischaemia (DCI) remains the single most important cause of morbidity and mortality in those patients who survive the initial bleed. The pathological mechanisms underlying DCI are still unclear and the calcium channel blocker nimodipine remains the only therapeutic intervention proven to improve functional outcomes after SAH. The recent failure of the drug clazosentan to improve functional outcomes despite reducing vasoconstriction has moved the focus of research into DCI away from cerebral artery constriction towards a more multifactorial aetiology. Novel pathological mechanisms have been suggested, including damage to cerebral tissue in the first 72 h after aneurysm rupture ('early brain injury'), cortical spreading depression, and microthrombosis. A greater understanding of the significance of these pathophysiological mechanisms and potential genetic risk factors is required, if new approaches to the prophylaxis, diagnosis, and treatment of DCI are to be developed. Furthermore, objective and reliable biomarkers are needed for the diagnosis of DCI in poor grade SAH patients requiring sedation and to assess the efficacy of new therapeutic interventions. The purpose of this article is to appraise these recent advances in research into DCI, relate them to current clinical practice, and suggest potential novel avenues for future research.

Keywords: cerebral vasospasm; cortical spreading depression; delayed cerebral ischaemia; early brain injury; microthrombosis; subarachnoid haemorrhage

Aneurysmal subarachnoid haemorrhage (SAH) is a devastating disease frequently leading to death or poor functional outcome. Although it only accounts for 3–5% of all strokes,[1] the economic cost of SAH is disproportionately high as it affects younger patients, who often require long-term care and cannot return to work. Only one-third of those patients who survive to discharge resume the same employment as before the event[2] and even those patients with 'good' functional outcomes are frequently left with significant residual neurocognitive deficits in areas such as memory, executive functioning, and language.[3 4]

Delayed cerebral ischaemia (DCI) is a clinical syndrome of focal neurological, cognitive deficits, or both that occurs unpredictably in ~30% of patients unpredictably 3–14 days after the initial haemorrhage.[5] While aneurysmal re-bleeding is still a significant complication in the hours following the initial bleed, DCI remains the single most important cause of mortality and morbidity in those patients who survive to definitive aneurysm treatment.[6]

Historically, it was widely considered that the primary mechanism underlying delayed neurological deterioration after SAH was narrowing of cerebral blood vessels (due to endothelial hypertrophy and vasoconstriction), leading to tissue ischaemia. This process was thought to be mediated by the presence of extravasated blood in the subarachnoid space. Arterial constriction visualized angiographically, in association with neurological deterioration seen clinically soon led to the use of the term 'vasospasm' to describe both the clinical and radiological changes. However, an emerging body of evidence now suggests that DCI is likely to have a multifactorial aetiology beyond pure cerebral arterial constriction. This has significant implications on the identification of patients at risk, diagnosis, and therapeutic interventions currently available for prophylaxis and treatment of DCI.

In the past, research into DCI has been complicated by the wide range of terms used to define the condition resulting in confusion regarding the underlying pathophysiology. The differing approaches to treating the ruptured cerebral aneurysm (either surgical clipping or endovascular coil embolization) have made comparison of trials investigating DCI difficult. In 2010, a consensus statement by a multidisciplinary group proposed new definitions for clinical deterioration caused by DCI and cerebral infarction after SAH (Table 1),[7] which will hopefully simplify study comparisons, standardize clinical endpoints, and allow accurate meta-analyses to be conducted. In 2011, the Neurocritical Care Society published consensus guidelines on the critical care management of patients after SAH.[8]

Table 1 Proposed definitions of DCI and cerebral infarction after SAH for use as an outcome event in clinical trials and observational studies[13]

Clinical deterioration caused by DCI
The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, or neglect), or a decrease of at least 2 points on the Glasgow coma scale (either on the total score or on one of the components)
This should
(1) Last for at least 1 h (2) Not be apparent immediately after aneurysm occlusion (3) Not be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies
Cerebral infarction
The presence of cerebral infarction on either:
(1) CT or MRI scan of the brain within 6 weeks after SAH (2) The latest CT or MRI scan made before death within 6 weeks after SAH (3) Proven at autopsy
This evidence must not be present on the CT or MRI scan between 24 and 48 h after early aneurysm occlusion and must not be attributable to other causes such as surgical clipping or endovascular treatment
Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal haematoma should not be regarded as cerebral infarctions from DCI

This review concentrates on clarifying the role of vasoconstriction in DCI, highlights novel theories regarding the pathogenesis behind DCI, and summarizes the evidence for current and new therapeutic strategies. Through this, we hope to explore unanswered questions and propose directions for future research into DCI.

Vasoconstriction and DCI

Acute clinical deterioration during the period after SAH has long been known to occur after aneurysmal rupture. Early case reports showed that some patients with early improvement in neurological state after SAH rapidly and unexpectedly deteriorated and died in the days after the initial SAH.[9] Although the cause of the initial bleed was identified as cerebral aneurysm rupture, the mechanism behind this subsequent deterioration was unclear. In 1949, post-mortem examination of 27 fatal cases of SAH demonstrated infarction remote from the site of the ruptured aneurysm, despite apparently patent cerebral vessels.[10] This was attributed to 'temporary spasm of the supplying vessels . . . even of those vessels remote to the aneurysm' and was the first suggestion that cerebral arterial vasoconstriction was linked to delayed clinical deterioration after SAH.

Radiological evidence of cerebral vasoconstriction in association with SAH in patients was first described in 1951 using serial carotid arteriograms.[11] Vessel narrowing was greatest near the site of the ruptured aneurysm and correlated with extravasated blood products. It was noted that vasoconstriction was rarely seen in angiograms performed 26 days post-SAH. The hypothesis was that after the initial bleed, 'vasospasm' of cerebral arteries might lead to impaired circulation in the territory of the brain supplied by the affected vessel. In 1978, a classification for SAH based on the pattern of blood distribution seen on computed tomography (CT) in a case series of 47 patients with SAH reported an almost exact correlation between the site of the major subarachnoid blood clots and the location of severe angiographic vasoconstriction.[12] Conversely, angiographic vasoconstriction was invariably absent in those patients with minimal subarachnoid blood load. Further angiographic evidence in almost 300 SAH patients showed that this vasoconstriction began day 3 post-SAH, was maximal at days 6–8, and had disappeared by day 12.[13] As a result of this work, the concept of extravasated blood from aneurysm rupture leading to a chain reaction of cerebral artery vasoconstriction, tissue infarction, and clinical deterioration has been widely held. However, although SAH is associated with cerebral vasoconstriction[13 14] and cerebral infarction after SAH is strongly associated with poor clinical outcomes,[15 16] the exact contribution of cerebral vasoconstriction in DCI remains unclear for the following reasons:

(1) Although the incidence of angiographic vasoconstriction during the second week post-SAH (the peak incidence) is around 70%,[5] the clinically detected incidence of DCI is only around 30%.[17]
(2) After SAH, patients can develop cerebral infarction in a vascular distribution unaffected by angiographic vasoconstriction[18] and cerebral infarction seems to exert a direct effect on poor outcome independent of angiographic vasospasm.[19]
(3) The temporal relationship between angiographic evidence of vessel constriction and DCI is poor.[20]
(4) The calcium channel antagonist nimodipine remains the only pharmacological treatment to improve outcomes from DCI, yet this benefit is achieved without angiographic evidence of cerebral vasodilation.[21 22]
(5) Treating angiographic vasospasm does not always lead to improvements in clinical and functional outcomes.[23 24]

Recently, a number of new theories have been proposed that may contribute towards understanding the pathophysiology behind DCI.

Novel theories regarding DCI pathogenesis

Early brain injury

Although the initial acute cerebral ischaemia caused by aneurysmal rupture accounts for the majority of the mortality and morbidity from SAH,[25] the pathophysiological changes that occur at this time remain poorly understood and few therapeutic or diagnostic interventions are available. 'Early brain injury' is a term that refers to the damage that occurs to the brain in the first 72 h after the initial bleed

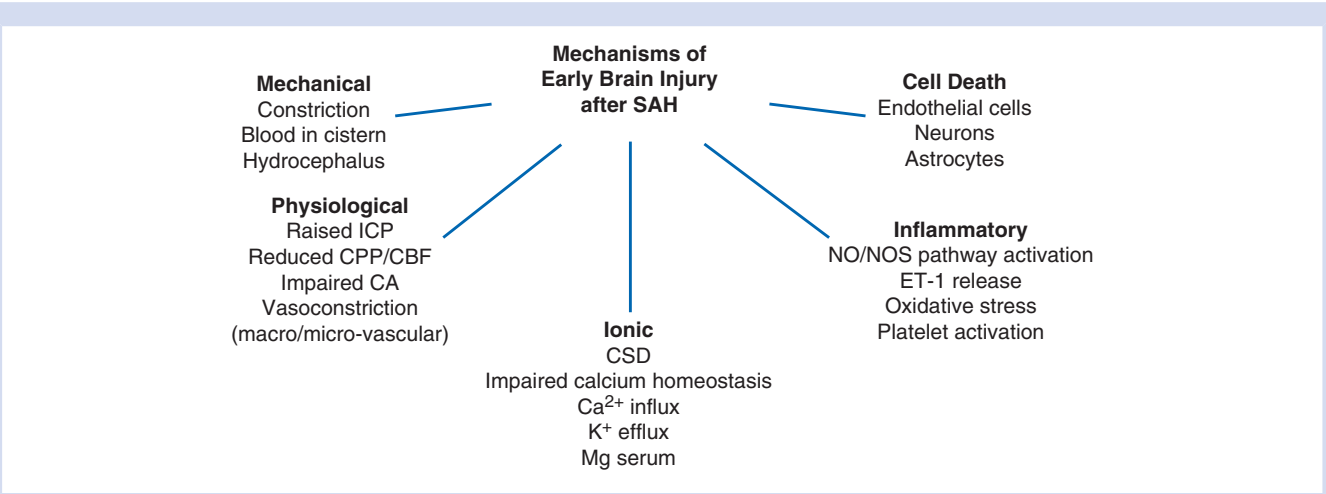

Fig 1 Mechanisms of early brain injury after SAH. ICP, intracranial pressure; CPP, cerebral perfusion pressure; CBF, cerebral blood flow; CA, cerebral autoregulation; CSD, cortical spreading depression; NO/NOS, nitric oxide/nitric oxide synthetase; ET-1, endothelin-1. Adapted, with permission, from Sehba and colleagues.[148]

(Fig. 1).[26] Although this is before the onset of DCI, it seems probable that the physiological changes occurring at this time may directly influence the likelihood and severity of later ischaemic complications in patients after SAH.

The majority of data on the pathophysiological changes that occur at the time of aneurysm rupture derives primarily from animal studies of SAH, mainly in rats. Although experimental results seem to mirror measurements in patients with aneurysmal re-bleeding and intracranial pressure (ICP) monitoring *in situ*, the majority of animal models rely on iatrogenic damage to cerebral vessels to simulate aneurysm rupture and induce subarachnoid bleeding. As a result, some authors have questioned the applicability of rat models to the study of SAH in humans,[27] and there is a need for new animal models of SAH with a high incidence of spontaneous cerebral aneurysm rupture.[28]

Initial physiological changes

At the time of the SAH, blood extravasates from a rupture in the aneurysm and leaks under high pressure into the subarachnoid space. The size of the rupture defect correlates with the volume of blood clot present.[29] Within minutes of aneurysm rupture, there is an associated rapid increase in ICP, with the rate of increase reflecting the severity of the initial bleed. This accounts for the 'thunderclap' headache seen clinically in patients and is often accompanied by syncope caused by a sudden reduction in cerebral blood flow (CBF) and cerebral perfusion pressure (CPP).[30] This sharp increase in ICP is thought to be a mechanism for arresting the initial aneurysmal bleed and preventing subsequent re-bleeding—so called 'brain tamponade'.[30] Putative causative mechanisms include increased intracranial volume secondary to the bleed, vasoparalysis (leading to increased cerebral blood volume), and cerebrospinal fluid (CSF) drainage obstruction due to blood clot.[31] There are two distinct patterns to this increase in ICP. In most patients, ICP increases to a value approximating diastolic arterial pressure, then decreases to slightly above baseline.[32] This is usually accompanied by small volume haemorrhage and the presence of cerebral oedema. The second pattern of ICP increase is less common and is characterized by a sustained increase in ICP due to enlarging haematoma or the development of acute hydrocephalus.[33 34] The peak ICP values at the time of aneurysmal rupture correspond to both the amount of blood released into the subarachnoid space and the rate of haemorrhage.[14 32 35] Marked acute cerebral vasoconstriction at this time has also been described that seems to occur independently of changes in CPP and ICP and is likely to contribute to the cerebral ischaemia from aneurysmal rupture.[14]

Cerebral oedema

Cerebral oedema is a common feature of both experimental and clinical subarachnoid haemorrhage. It is evident on admission CT scans in 6–8% of patients[6 36] and develops over the first 6 days in an additional 12%.[36] After SAH, there is substantial damage to blood–brain barrier integrity due to apoptosis of endothelial cells and perivascular astrocyte cell death.[37]

Cerebral autoregulation

Acute impairment of cerebral autoregulation is seen as a consequence of the initial aneurysmal rupture.[38 39] Cerebral autoregulation is the inherent ability of blood vessels to maintain CBF constant over a wide range of arterial pressure levels by means of complex myogenic, neurogenic, and metabolic mechanisms.[40] In humans, CBF autoregulation typically operates between mean arterial pressures of ~60 and 150 mm Hg.[41] If these autoregulatory mechanisms are disrupted, CBF becomes dependent on CPP and blood viscosity and changes in systemic arterial pressure

and ICP can worsen cerebral oedema and brain tissue ischaemia.

Inflammation and oxidative stress

There is evidence to suggest early activation of inflammatory pathways after aneurysmal rupture and that the extravasated blood is responsible for a cascade of reactions involving the release of pro-inflammatory and vasoactive factors.[42] An early increase in pro-inflammatory cytokines including tumour necrosis factor-α, interleukin-6, and interleukin-1 receptor antagonist has been documented in both serum and CSF of patients after SAH, and correlates with acute and DCI and poor outcome.[43 44]

Cortical spreading depression and DCI

Over the last few years, cortical spreading depression (CSD) has been identified as a potential pathophysiological mechanism contributing to DCI. The term describes a depolarization wave in cerebral grey matter that propagates across the brain at 2–5 mm min^{-1} and results in depression of evoked and spontaneous EEG activity.[45] First demonstrated experimentally in the 1940s in rabbit cortex, the process was originally regarded as experimental artifact with little relevance to neurological disease in humans. Recently, however, there has been a resurgence of interest in CSD. Electrocorticographic recordings from invasive subdural recording strips, combined with laser Doppler measurements of regional CBF have allowed accurate quantification of the vascular changes associated with CSD. As a result, it has been implicated in the pathophysiology of a number of neurological diseases, including migraine,[46] malignant hemispheric stroke,[47] traumatic brain injury,[48] and DCI after SAH.[49]

To demonstrate CSD experimentally in healthy brain tissue, either mechanical or electrical stimulation of the cortex is required.[50] Propagation of the CSD wave silences spontaneous and evoked synaptic activity in the brain for 5–15 min, and is followed by spontaneous return to normal function.[51] Characteristic cerebrovascular changes include a brief period of vasoconstriction before the CSD, vasodilation accompanying the spreading wave front followed by delayed tissue hypoperfusion after the wave.[52]

In contrast to this, in the injured brain, CSDs can occur spontaneously and recovery of normal function can be prolonged, contributing to tissue ischaemia. The classic pattern of transient, hyperperfusion accompanying the CSD wave front seems to be different. In SAH, there is good evidence from animal models and patient studies that CSDs occur after the initial bleed.[49 53] CSDs can occur as isolated events or as clusters and there appear to be three distinct vascular responses to CSD in SAH: physiological (spreading hyperperfusion), absent (no change from baseline), and inverse haemodynamic (spreading ischaemia) (Fig. 2).[49] Spreading ischaemia was first described in a rat model of DCI and results from local microvascular dysfunction. It is thought that with each depolarization, there is an associated profound hypoperfusion of the cortex due to vasoconstriction.[54] With each wave of spreading depression, the hypoperfused segments of the cortex do not get the chance to recover and are therefore exposed to recurrent episodes of tissue ischaemia.

The incidence of CSDs measured in patients after SAH also seems to correlate with the time frame for the development of DCI, with data from one study demonstrating that 75% of all CSDs recorded occurred between the fifth and seventh day after SAH.[55] CSDs also seem to occur in the absence of angiographic vasoconstriction. Despite placement of nicardipine pellets around the middle cerebral artery (at the time of surgery) to minimize proximal vasoconstriction, spontaneous depolarizations still occurred in 10 out of 13 patients,[56] casting further doubt on the exact nature of the contribution of proximal vessel constriction to DCI.

Microthrombosis

A number of studies have shown that the coagulation cascade is activated early after the initial SAH and importantly, preceding the onset of DCI. This is most likely as a result of endothelial damage from aneurysm rupture and subsequent acute cerebral ischaemia and there is serological, clinical, and post-mortem evidence that this early activation is an early predictor of both DCI and cerebral infarction (Fig. 3).

Serological studies of patients after SAH have demonstrated activation of the coagulation cascade and impairment of the fibrinolytic cascade. Levels of platelet-activating factor start to increase within 4 days after SAH, suggesting increased platelet activation and adhesion.[57] Elevated concentrations of von Willebrand factor and CSF tissue factor (the primary initiator of coagulation) in the first few days after SAH have been shown to predict the occurrence of DCI, cerebral infarction, and poor outcome.[58 59] Other studies have shown that overactive inhibition of fibrinolysis is associated with DCI[60] and that elevated levels of fibrin degradation products and D-dimer in the CSF of patients after SAH are associated with DCI, cerebral infarction, and poor outcome.[61]

Further evidence to support the role of microthrombosis in DCI is provided by trans-cranial Doppler (TCD) detection of micro-emboli. A prospective study using TCD showed that micro-embolic signals were present in up to 70% of SAH patients, with a non-significant trend towards an increased incidence of micro-emboli in those patients who went on to develop DCI.[62]

Post-mortem studies of SAH patients have also demonstrated evidence of microthrombi. Patients with DCI have significantly more microthrombi in areas showing cerebral infarction than those patients that die from aneurysmal re-bleed or hydrocephalus.[63] Microthrombosis also correlated with the amount of overlying free subarachnoid blood and clinical and pathological signs of ischaemia.[64] Interestingly, a post-mortem study into microthrombosis after SAH showed that while cortical ischaemic lesions were present

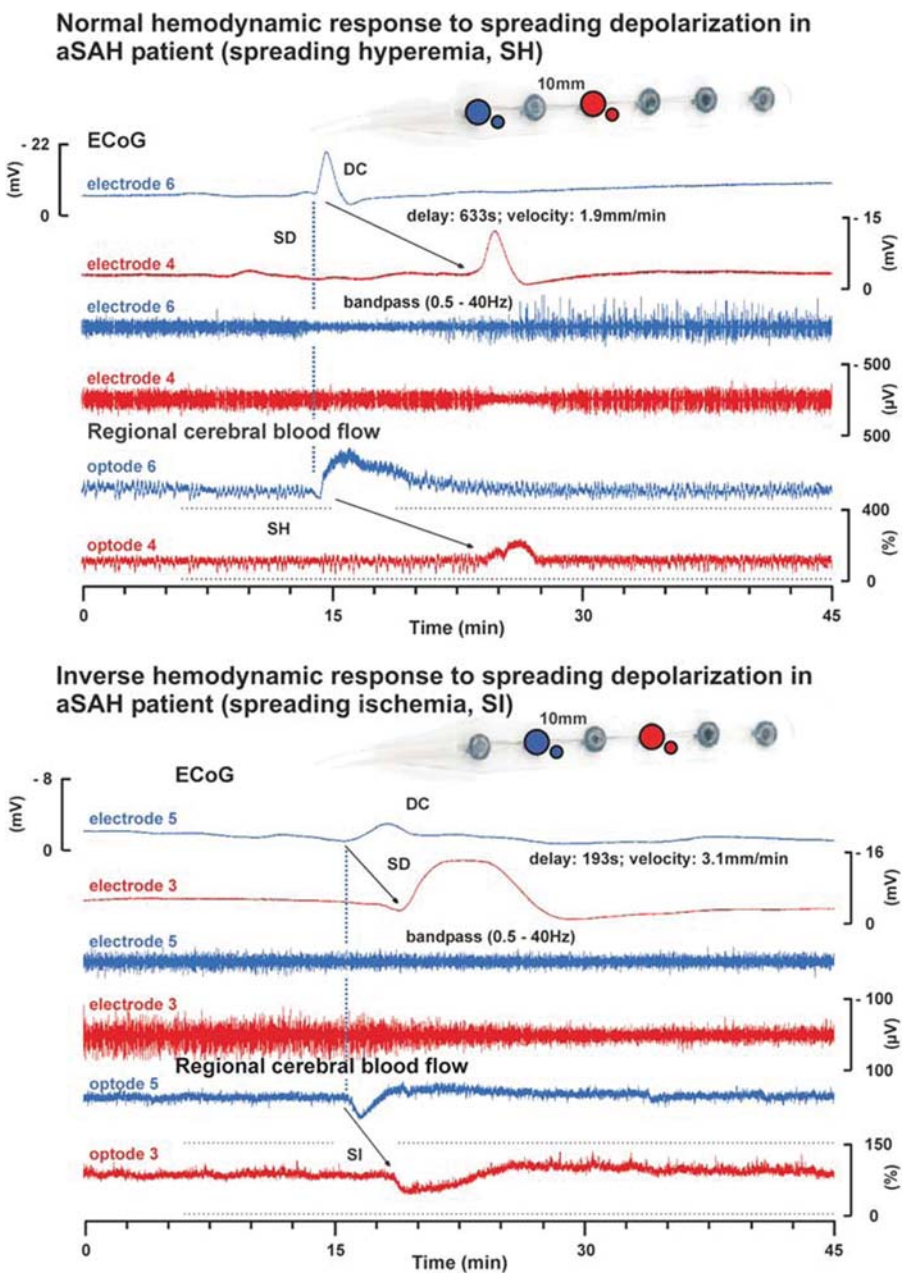

Fig 2 Normal and pathological response to cortical spreading depression (CSD) in patients with aneurysmal subarachnoid hemorrhage (aSAH). The upper half of the figure shows the normal hemodynamic response to spreading depolarization (CSD) in the human brain in a patient with aSAH. The subdural opto-electrode strip is shown in the upper right corner. The six traces represent simultaneous recordings of a single spreading depolarization that propagates from opto-electrode 6 (blue) to 4 (red). The calibration bar of trace 4 also applies to trace 3 and that of trace 6 also applies to trace 5. The four upper traces identify the spreading depolarization electrophysiologically. Traces 1 and 2: direct current (DC) electrocorticogram (ECoG) with negative shift of spreading depolarization. Traces 3 and 4: band-pass filtered ECoG (0.5 to 45 Hz) with spreading depression of activity. The spreading depolarization propagates at a rate of about 1.9 mm min^{-1} assuming an ideal linear spread along the recording strip. Traces 5 and 6: Normal spreading hyperaemia in response to spreading depolarization recorded by laser-Doppler flowmetry as reported previously (Dreier *et al.*, 2009[49]). The lower half of the figure demonstrates the inverse hemodynamic response to spreading depolarization in another patient with aSAH. In this case, the spreading depolarization propagates from opto-electrode 5 (blue) to 3 (red) (propagation rate: 3.1 mm min^{-1}). The high-frequency activity is already suppressed by a preceding CSD at electrode 4 (trace 9), when depression of activity is induced by spreading depolarization at electrode 5 (trace 10). Traces 11 and 12: typical inverse haemodynamic response to spreading depolarization as characterized by a severe decrease of regional cerebral blood flow (CBF) in response to the depolarization. Such severe decrease of regional CBF in response to CSD is termed spreading ischaemia. The prolonged negative cortical DC shift (compare trace 8) is the defining electrophysiological feature for the inverse haemodynamic response. It indicates that the hypoperfusion is significant enough to produce a mismatch between neuronal energy demand and supply (Dreier *et al.*, 1998,[149] 2009[49]). Figure and text adapted from Lauritzen *et al.*, 2011[51] JCBFM. Reprinted by permission from Macmillan Publishers Ltd, © 2011.

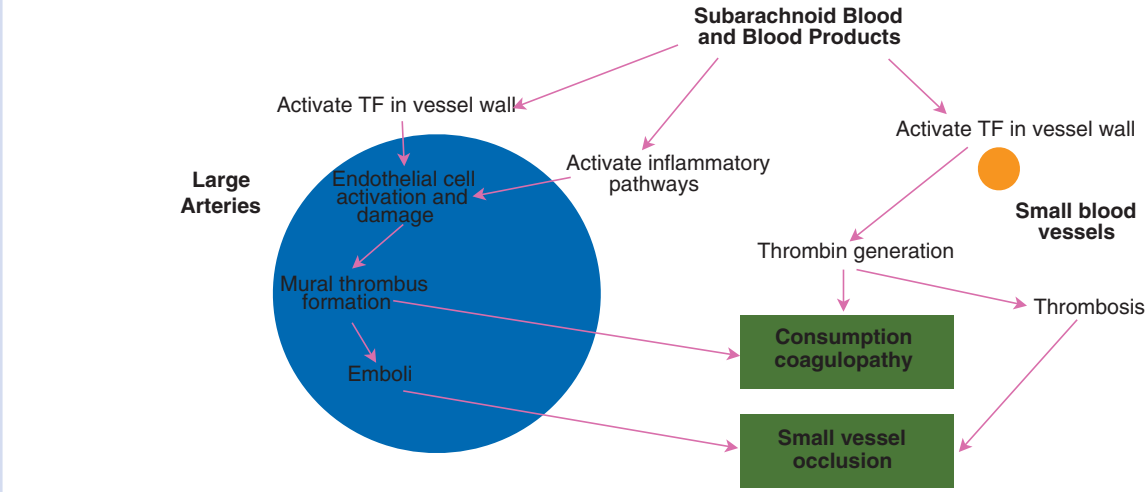

Fig 3 Potential mechanisms of microthrombosis formation after SAH. TF, tissue factor. Adapted, with permission, from Stein and colleagues.[64]

in 77% of patients, there was no significant association between the presence of these lesions and angiographic vasospasm or aneurysm location.[65]

Collateral cerebral circulation

Although the importance of the pathophysiological recruitment of collaterals in the setting of chronic haemodynamic insufficiency (such as carotid artery stenosis) has been well documented,[66 67] the impact of collateral flow in acute cerebral ischaemia is less clear. The cerebral collateral circulation consists of a subsidiary network of vascular channels that stabilize CBF when principal conduits fail.[68] Primary collaterals include the anterior and posterior communicating arteries of the circle of Willis, which immediately divert cerebral blood flow to ischaemic regions through existing anastomoses. Secondary collaterals include leptomeningeal vessels and reversal of blood flow in the ophthalmic artery, and are normally only recruited when the primary collateral circulation is inadequate.

Early clinical improvement in ischaemic stroke patients is linked to the presence of cerebral collateral blood supply.[69] Magnetic resonance imaging (MRI) studies of patients with ischaemic stroke have also shown that collateral flow in the circle of Willis is associated with a reduction in the prevalence of ischaemic lesions and minimizes the degree of residual tissue hypoperfusion after arterial occlusion.[70] Little attention is generally paid to pre-treatment collateral status in clinical practice in SAH patients. This is despite considerable heterogeneity in the presence of collateral vessels demonstrated in patients with ischaemic stroke.[70 71]

Following SAH, we speculate that patients with greater capacity for collateral flow may suffer less initial ischaemic damage from early brain injury. Furthermore, recruitment of collateral vessels may be the mechanism behind the reversal of neurological deficits seen with induced hypertension as part of triple-H therapy. Clinical assessment of collateral flow is usually limited to CT or MR angiography with the former requiring ionizing radiation and both requiring i.v. contrast. Improvements in MRI sequences now allow the non-invasive assessment of flow in the circle of Willis and other cerebral collateral pathways such as the ophthalmic artery. Identifying those patients with poor collateral flow may enable earlier treatment strategies, such as induced hypertension, to improve cerebral perfusion.

How have clinical therapeutic interventions aided the understanding of DCI?

At present, the majority of therapeutic strategies targeting DCI are focused on reducing secondary ischaemic brain injury and treating cerebral vasoconstriction. However, the exact role of cerebral vasoconstriction remains unclear and as a result, the rationale behind some treatment strategies requires further examination.

Clazosentan

Clazosentan is an endothelin (ET)-A antagonist that was heralded as a potential pharmacological treatment for DCI after SAH. As ET is known to play a key role in maintaining vascular tone in blood vessels, it was hypothesized that pharmacological antagonism of ET receptors might be of therapeutic benefit in reducing cerebral vasospasm and DCI. The ET receptor antagonist TAK-044 was studied but showed no beneficial effects on DCI, cerebral infarction, or functional outcome at 3 months (as measured by the Glasgow outcome score). This was attributed to non-selective antagonism of both ET-A and ET-B receptors.[72] Further studies using clazosentan, a selective ET-A receptor antagonist, showed promise with a reduction in the frequency and severity of vasospasm after SAH[73] and a reduction in vasospasm-associated impaired cerebral perfusion.[74]

Unfortunately, the subsequent multicentre CONSCIOUS-1 randomized control trial (RCT) showed that despite significant reductions in angiographic cerebral vasoconstriction, clazosentan failed to show a significant effect on morbidity and mortality and no obvious effect on functional outcome.[23] Furthermore, clazosentan showed no significant benefit in a subgroup of SAH patients treated with surgical clipping, leading to the early termination of the CONSCIOUS-2 trial[75] and the cancellation of the planned CONSCIOUS-3 trial in SAH patients treated with endovascular coiling.[76] From the CONSCIOUS trials, it would appear that, despite questions raised regarding study design, duration of treatment, and scoring scales,[77] the pathophysiological mechanism behind DCI is likely to extend beyond pure large vessel vasoconstriction. The effect of clazosentan on the cerebral microcirculation is unclear and the drug seems to have little effect on the coagulation disturbances seen after SAH such as microthrombosis.[78]

Nimodipine

Despite extensive research into pharmacological treatment of DCI, the L-type dihydropyridine calcium channel antagonist nimodipine remains the only intervention to consistently reduce the incidence of DCI and improve outcomes after SAH. Calcium plays a critical role in cellular communication and regulation and is important for the maintenance of normal cerebral vascular tone.[79] Uncontrolled intracellular shifts in calcium concentration associated with cerebral ischaemia cause irreversible cell destruction and death, especially in the central nervous system[80] and as a result, calcium is likely to play an important role in initiating, mediating, and propagating damage to cells after SAH.

Nimodipine was first tested as a treatment for DCI due to its preferential vasodilation of the cerebral circulation and experimental work showing reduced impairment of post-ischaemic reperfusion.[81] The largest clinical trial of nimodipine on DCI (the British Aneurysm Nimodipine Trial) randomized patients to either oral nimodipine 60 mg at 4 h intervals or placebo for 21 days after SAH[82] and showed significant reductions in both the incidence of cerebral infarction and poor neurological outcomes at 3 months post-SAH. Further meta-analyses including a Cochrane review in 2007[83] have echoed these findings and led to oral nimodipine becoming a standard of care for patients from the time of the initial haemorrhage.[22 83]

The precise mechanism behind the beneficial effects of nimodipine remains unclear and seems independent of any action on large vessel angiographic vasoconstriction.[21] It may be that nimodipine has a neuroprotective effect in SAH by blocking calcium influx after tissue ischaemia at a neuronal level.[84] However, as nimodipine does not exert a beneficial effect on other diseases that lead to cerebral ischaemia such as ischaemic stroke[85] or traumatic brain injury,[86] it seems likely that it acts on a mechanism specific to SAH. A systematic review of calcium antagonists showed that nimodipine significantly increases endogenous fibrinolytic activity and that this effect is not found with other calcium antagonists such as phenylalkylamines.[87] This may act to reduce the incidence of microthrombosis after SAH. Finally, there is evidence that nimodipine antagonizes cortical spreading ischaemia in rats,[88] and this may be of importance, given the potential role of CSD in the pathogenesis of DCI.

Induced hypertension, hypervolaemia, and haemodilution ('triple-H therapy')

Haemodynamic strategies to induce hypertension, hypervolaemia, and haemodilution remain the mainstay of the neurocritical care management of DCI. However, despite its widespread use, much of the literature supporting triple-H therapy is only of moderate quality with RCTs only addressing prophylactic use.

The physiological rationale behind triple-H therapy is based on the haemodynamic consequences of cerebral arterial vasoconstriction. As vessel diameter decreases, cerebrovascular resistance shifts from smaller penetrating arterioles to the major branches of the circle of Willis. As a result, brain tissue supplied by these narrowed proximal branches loses its capacity for autoregulation and CBF varies directly with systemic arterial pressure according to the Hagen–Poiseuille law. Therefore, given that the vessel diameter is fixed, the only variables that can potentially be manipulated to improve CBF in patients after SAH are the pressure gradient (i.e. systemic arterial pressure) and blood viscosity (i.e. haematocrit).

Early anecdotal evidence suggested that hypotension could lead to neurological deficits in patients after 'cerebrovascular accidents'.[89] This seemed especially significant in those patients where hypotension was associated with evidence of structural narrowing of major cerebral blood vessels. As a result, induced hypertension was tried in patients after SAH with an early case series showing reversal of neurological deficits in six out of seven patients through the use of norepinephrine to increase arterial pressure and volume expansion with colloid.[90] A larger retrospective review of induced hypertension and volume expansion in 58 patients supported these findings.[91] However, there were significant complications including aneurysmal re-bleeding (19%), pulmonary oedema (17%), dilutional hyponatraemia (3%), and coagulopathy (3%).

Recent studies of triple-H therapy in DCI have attempted to use physiological outcome measures such as brain tissue oxygenation and CBF to assess the individual contribution of each of the components of haemodynamic augmentation, that is, induced systemic hypertension (either through vasopressors or inotropes), volume expansion, and haemodilution. A Cochrane review of three studies analysing the evidence supporting volume expansion therapy concluded a lack of benefit, and that hypervolaemia could potentially increase complications after SAH.[92] A recent meta-analysis found no good evidence for a positive effect of triple-H therapy or any of its components on CBF after SAH.[93]

Haemodilution did not increase CBF and hypervolaemia was only beneficial in one of seven trials.

The consensus guidelines recently published by the Neurocritical Care Society[8] make a number of recommendations regarding each of the individual components of triple-H therapy. It seems that any benefit that might occur from haemodynamic manipulation of SAH patients is likely to primarily derive from increasing or stabilizing systemic arterial pressure and avoidance of hypovolaemia. Owing to its widespread use, randomized outcome studies of induced hypertension and untreated control groups are now unlikely. Further research is needed into the timing and effects of different pharmacological and mechanical strategies for inducing hypertension on outcomes from DCI.

Magnesium

Magnesium is a non-competitive calcium channel antagonist and potent vasodilator with known neuroprotective properties. Hypomagnesaemia occurs in more than 50% of patients with SAH, is related to severity of bleed, and is predictive of DCI.[94] As a result, a number of studies have investigated the role of i.v. magnesium therapy in preventing and treating DCI.

In animal models of SAH, magnesium reverses delayed cerebral arterial vasoconstriction and reduces the size of ischaemic lesions.[95] There is evidence to suggest that magnesium reduces the rate and frequency of CSD.[96] However, the only phase III RCT conducted to date [Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Haemorrhage (IMASH) trial] showed no difference in the proportion of patients with a favourable outcome at 6 months or in the incidence of DCI or cerebral infarction. A *post hoc* analysis showed an association between high plasma magnesium concentrations and worse clinical outcomes.[97]

The results of this trial have considerably dampened enthusiasm for the routine use of magnesium and an updated systematic review and meta-analysis further demonstrated no beneficial effect of magnesium in DCI.[98] As a result, it has been recommended in the Neurocritical Care Society guidelines that magnesium should not routinely be given to patients after SAH (although hypomagnesaemia should be avoided).[8]

Statins

There has been interest in using statins in SAH, for both the prevention and treatment of DCI. The pleiotropic vascular effects of statins include beneficial actions on endothelial inflammation,[99] oxidative stress,[100] and the inhibition of platelet adhesion and aggregation[101] and these underlie the benefits they exert on atherosclerotic cardiovascular disease. Given that statins are relatively safe, cheap, and easy to administer, they seem a logical intervention to trial in the prevention of DCI.

Animal studies have demonstrated that statins may ameliorate early brain injury after experimental SAH[102] and improve neurocognitive outcomes.[103] To date, four prospective, randomized, placebo-controlled trials have been published evaluating the efficacy of statins in the prevention of DCI. These investigated a combined total of 190 patients with three of the studies trialling simvastatin 80 mg for 14–21 days[104–106] and one study trialling pravastatin 40 mg for a maximum of 14 days.[107] Although the first two published studies reported beneficial effects in reducing episodes of DCI, TCD vasospasm, and mortality, these findings were not found in the more recent studies. There was also significant variation in the proportion of clipped and coiled patients and high-grade patients between the studies making comparison difficult. Additionally, although up to 50% of patients in the pravastatin trial did not complete the course of treatment, results were still analysed on an intention-to-treat basis.[107] A recent meta-analysis of RCTs included these four studies and reported that statins had no significant effect on any of the relevant outcomes, including clinical episodes of DCI, mortality, poor neurological recovery, and TCD vasospasm.[108]

Given the efficacy of statin pre-treatment in animal models,[109] the impact of prior statin use in patients presenting with SAH has also been investigated in observational studies. Two studies demonstrated reductions in DCI and improved clinical outcomes in SAH patients with previous statin use.[110 111] However, continuity of statin therapy on admission was not clearly discussed in either study and further studies have shown either no benefit or increased risk of DCI in patients pre-treated with statins, although this latter finding was reported as being caused by statin withdrawal on admission.[112 113]

Although statin therapy seems safe post-SAH in statin-naïve patients, it remains unclear whether statins exert a beneficial effect in preventing DCI and improving clinical outcomes. The Neurocritical Care Society Guidelines recommend that patients on statins before presentation with SAH should have their medication continued in the acute phase but only suggest that acute statin therapy 'may be considered' in statin-naïve patients.[8] Hopefully, the results of a larger, prospective randomized controlled study—the Simvastatin in Aneurysmal Subarachnoid Haemorrhage ('STASH') Trial—that has recently restarted patient recruitment should help clarify whether statins should be routinely given to all patients after SAH.[114]

Anti-coagulant/anti-fibrinolytic therapy

As activation of the coagulation cascade and microthrombi may play a role in the pathogenesis of DCI, attention has focused on drugs targeting these processes. Aspirin was used in an attempt to reduce DCI by reducing platelet adhesion and aggregation. A systematic review of five trials with a total of 700 patients suggested a reduction in the risk of DCI in SAH patients. However, an RCT investigating the effect of 100 mg aspirin was stopped early as an interim analysis suggested that the probability of a beneficial effect was negligible.[115] Although a Cochrane review in 2007 suggested a trend towards better outcome in patients treated with anti-

platelet agents, this was non-significant and accompanied by the possibility of an increase in the risk of haemorrhagic complications.[116]

The role of low molecular weight heparins (LMWHs) in DCI has also been investigated. The anti-coagulant activity (antagonism of antithrombin III) of LMWH may prevent the formation and spread of microthrombi and there is evidence of neuroprotective effects. They act on complement and neutrophils to reduce cerebral inflammation in response to ischaemic lesions,[117 118] have anti-oedema properties,[119] and may reduce intra-neuronal calcium release after ischaemic injury.[120] However, two large placebo-controlled RCTs studying enoxaparin and DCI demonstrated contradictory results,[121 122] and further, large, multicentre trials are required to clarify whether these drugs have a beneficial effect on reducing DCI.

A Cochrane review of anti-fibrinolytic therapy for the prevention of aneurysmal re-bleeding showed that reductions in mortality from re-bleeding were offset by an increase in poor outcome from DCI.[123] The potential of intrathecal fibrinolysis has been investigated and although a systematic review showed a significant risk reduction in DCI and poor outcome, only one of the nine studies was an RCT and its role remains unclear.[124]

Future directions for DCI research

Determining the genetic determinants of DCI

It seems logical that genotypic variability may define the susceptibility of individual patients to both the initial ischaemic injury caused by aneurysmal rupture and subsequent secondary damage caused by DCI. Genetic predisposition to the individual pathophysiological mechanisms that may underlie DCI such as cerebral vasoconstriction, CSD, and microthrombosis may vary between individual patients.

Endothelial nitric oxide synthase

Much of the research into genetic influences underlying DCI has focused on reducing cerebral vasoconstriction—in particular through targeting the gene encoding the endothelial isoform of nitric oxide synthase (eNOS). Nitric oxide (NO) inhibits smooth muscle proliferation and inflammation—both pathophysiological features of the cerebral vasoconstriction seen after SAH. There is evidence that certain eNOS polymorphisms are significantly associated with angiographic cerebral arterial narrowing after SAH, and also cerebral aneurysm rupture.[125 126] However, others have shown no association between eNOS polymorphisms and cerebral infarction or the incidence of clinical deterioration in patients.[127] This suggests that the influence of eNOS polymorphisms is primarily limited to vascular constriction and further questions the significance of the contribution of vessel narrowing to DCI.

Apolipoprotein E

The association between apolipoprotein E (ApoE) and neurocognitive outcomes after SAH has been investigated. ApoE is a carrier protein that combines with lipids to form lipoprotein particles which is involved in the metabolism and transport of lipids in the central nervous system. Three common alleles of the ApoE gene are found in humans—ε2, ε3, and ε4. The presence of the ε4 allele is known to be associated with increased risk of developing Alzheimer's disease[128] and poor outcomes after traumatic brain injury,[129] and intracerebral haemorrhage,[130] although this association does not seem to extend to ischaemic stroke.[131]

The association between ApoE and DCI is conflicting, with an animal model of SAH showing that mice expressing the ε4 protein have greater cerebral vasoconstriction, functional deficit, and mortality after SAH than those with the ε3 protein.[132] However, in SAH patients, an association between ApoE4 and poor functional outcomes[133] and a meta-analysis of eight observational studies concluded that the expression of the ε4 allele is associated with an increased risk of poor outcome and delayed ischaemia.[134]

The most recent prospective study found that neither the ε2 nor the ε4 allele was associated with infarction or poor outcome and concluded that ApoE polymorphisms have no prognostic value for outcome after SAH.[135] The largest association study of ApoE and SAH showed no significant difference between the presence of the ApoE4 genotype and functional outcomes at 3 and 6 months when controlling for age, size of haemorrhage, and clinical severity of SAH.[136] However, when severity of cerebral arterial vasospasm was controlled between the groups, individuals with the ε4 allele had worse functional outcomes at both time points. This suggests that the ε4 allele may not directly influence cerebral vasoconstriction and may instead act to modulate the response of brain tissue to ischaemia.

Although a number of theories have been proposed including protection from oxidative injury[136] and suppression of lymphocyte proliferation and glial cytokine secretion,[137] further work is required to clarify the specific mechanism by which ApoE is associated with DCI and whether certain alleles can be used to reliably identify patients at risk. Further investigation of the impact of genetic influences in response to therapeutic interventions such as induced hypertension, statins, and nimodipine is required, in addition to further research into those genes that regulate inflammation and fibrinolysis.

The interaction between anaesthetic agents and CSD

Many SAH patients require surgical, endovascular, or neurocritical care interventions where significant quantities of anaesthetic sedative agents are required either to facilitate mechanical ventilation or control ICP. Although current evidence indicates that volatile agents, barbiturates, and propofol may have neuroprotective actions, the interaction between these sedative agents and DCI remains unclear. If CSD plays some role in the pathogenesis of DCI, the choice of sedative agent may be important. Most of the research on anaesthetic agents and CSD has focused on the effect of volatile inhalation agents on animal models of brain

injury, looking for changes in CSD frequency and intensity. Studies in rats have shown that halothane, and to a lesser extent isoflurane and nitrous oxide, protect against the initiation of CSDs in the cortex[138] and that nitrous oxide decreases CSD propagation speed and duration.[139] Increasing the concentration of volatile anaesthetic agents results in a dose-dependent reduction in CSD frequency,[140] possibly linked to the increase in CBF seen with most volatile anaesthetic agents. Although the use of volatile anaesthetic agents in the intensive care or emergency room setting is rare, the AnaConDa device (anaesthetic conserving device) has enabled their use in the treatment of refractory status asthmaticus[141] and may offer a potential solution in SAH.

There is currently no data published comparing the effects of inhalation and i.v. agents on CSD. This is especially important as i.v. agents such as propofol, fentanyl, and remifentanil are extensively used in both neuroanaesthesia and neurocritical care. The effect of propofol on CSD has yet to be formally investigated, although evidence that propofol, and thiopental, attenuate gap–junction coupling[142] and that thiopental may reduce the incidence of CSD *in vitro* may be relevant.[143] Ketamine, known to increase ICP and therefore rarely used in the management of patients with SAH, may also behave like volatile agents and block CSD.[144] This evidence has been reinforced by case reports showing the inhibition of CSD and restoration of normal electrocorticographic activity with ketamine in intracranial haemorrhage.[145] As a result, more research into the choice of sedative agent and CSD is needed.

Biomarkers for DCI

The delay between aneurysmal rupture and the onset of DCI offers a unique opportunity to apply a therapeutic intervention to patients after SAH. The recent consensus definitions quoted earlier in this article should be commended for providing a clear 'threshold' for the clinical diagnosis of DCI in patients. However, given that the majority of patients with poor grade SAH require sedation and mechanical ventilation, diagnosis of DCI by clinical assessment is often impossible. It also seems logical to suggest that DCI is in fact a spectrum of disease with patients exhibiting varying degrees of severity. If this is the case, then the reliance of this clinical definition on a change in Glasgow coma scale, which is relatively insensitive to subtle changes in neurocognitive function, may leave some patients with sub-threshold DCI undiagnosed and untreated.

Identifying objective biomarkers for DCI therefore remains a key research priority. Unfortunately, the uncertain pathophysiology of DCI has made this process difficult with no specific or sensitive serum or CSF biomarker currently available. Measures of axonal degeneration such as CSF neurofilament heavy chains (NfH) have shown some early promise in identifying secondary ischaemic damage caused by DCI and may be useful in those patients who require CSF diversion on the neurocritical care unit.[146] Other serum markers such as high-sensitivity C-reactive protein may identify the inflammatory activation that is specifically related to DCI.[147]

Currently, the invasive nature of the monitoring required negates investigation of the incidence of CSD in those patients who do not require neurosurgical intervention. Quantifying the vascular changes associated with CSD—such as the suppression of low-frequency vascular oscillations[49]—non-invasively using MRI or near-infrared spectroscopy may offer a surrogate measure of CSDs in those patients with less severe grade SAH who undergo endovascular aneurysm treatment.

Evidence suggests that CSDs are associated with cerebral ischaemia after poor grade SAH and are likely to contribute towards DCI. However, the absence of non-invasive biomarkers of CSD means the overall frequency of CSDs in patients after SAH remains unknown and the role of inhalation and i.v. anaesthetic agents and also treatments such as nimodipine and magnesium on CSD requires further investigation. Future studies into DCI will benefit from clear consensus definitions and clinical endpoints and should focus on the following questions that currently remain unanswered:

(1) Why is nimodipine the only pharmacological treatment to reduce the incidence of DCI and improve ischaemic outcomes and what is the mechanism behind this effect?
(2) Can we develop more accurate experimental models of spontaneous aneurysm rupture that might replicate the physiological changes more accurately?
(3) Does the initial period post-aneurysmal rupture offer a diagnostic and therapeutic target for interventions aimed at reducing the incidence of DCI and improving outcomes?
(4) How important is CSD in the aetiology of DCI and what effect do current therapeutic interventions used in SAH have on its incidence and progression?
(5) Is it possible to identify objective biochemical, electrocortical, or neuroimaging biomarkers of DCI that will allow earlier identification of those at risk (especially in sedated patients) and act as a target for future research into novel treatments?
(6) Can we influence DCI at a genetic level both to identify patients at risk and to guide application of therapeutic interventions?

In conclusion, DCI remains the major cause of mortality and morbidity in those patients who survive the initial bleed to hospital treatment. It now seems clear that DCI has a multifactorial aetiology beyond pure cerebral vasoconstriction and that future management strategies are likely to be based on combination therapies targeting vasoconstriction, disturbed neuronal function, and disturbed neurovascular coupling.[49] The interval between aneurysmal rupture and the onset of DCI provides a window for the application of preventative pharmacological therapies. Currently, however, the majority of therapeutic strategies in clinical use remain focused on improving cerebral perfusion in patients *after* the onset of DCI symptoms. More research is therefore required into the acute changes in cerebral physiology

occurring in the first 72 h after SAH that may offer potential diagnostic and therapeutic targets for DCI in the future.

Declaration of interest

None declared.

Funding

The authors' research into subarachnoid haemorrhage is supported by a *BJA*/RCOA grant from the National Institute of Academic Anaesthesia. M.J.R. is supported by the NIHR Oxford Biomedical Research Centre and the Oxford University Clinical Academic Graduate School. K.T.S.P. and M.J.R. are supported by the Medical Research Council, UK.

References

1 Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. *Stroke* 1997; **28**: 491–9

2 Passier PECA, Visser-Meily JMA, Rinkel GJE, Lindeman E, Post MWM. Life satisfaction and return to work after aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis* 2011; **20**: 324–9

3 Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *Stroke* 2010; **41**: e519–36

4 Scott RB, Eccles F, Molyneux AJ, Kerr RSC, Rothwell PM, Carpenter K. Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: neuropsychological outcomes from the International Subarachnoid Aneurysm Trial (ISAT). *Stroke* 2010; **41**: 1743–7

5 Dorsch NW, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage Part I: incidence and effects. *J Clin Neurosci* 1994; **1**: 19–26

6 Kassell N, Torner J, Clarke Haley E Jr, *et al.* The international cooperative study on the timing of aneurysm surgery. *J Neurosurg* 1990; **73**: 18–36

7 Vergouwen MDI, Vermeulen M, van Gijn J, *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

8 Diringer MN, Bleck TP, Claude Hemphill J, *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

9 Beadles C. Aneurisms of the larger cerebral arteries. *Brain* 1907; **30**: 285–336

10 Robertson EG. Cerebral lesions due to intracranial aneurysms. *Brain* 1949; **72** (Pt 2): 150–85

11 Ecker A, Riemenschneider P. Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms. *J Neurosurg* 1951; **8**: 660–7

12 Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery* 1980; **6**: 1–9

13 Weir B, Grace M, Hansen J, Rothberg C. Time course of vasospasm in man. *J Neurosurg* 1978; **48**: 173–8

14 Bederson JB, Levy AL, Ding WH, *et al.* Acute vasoconstriction after subarachnoid hemorrhage. *Neurosurgery* 1998; **42**: 352–60

15 Fergusen S, Macdonald RL. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2007; **60**: 658–67

16 Vergouwen MDI, Etminan N, Ilodigwe D, Macdonald RL. Lower incidence of cerebral infarction correlates with improved functional outcome after aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 2011; **31**: 1545–53

17 Dorsch N. A clinical review of cerebral vasospasm and delayed ischaemia following aneurysm rupture. *Acta Neurochir Suppl* 2011; **110** (Pt 1): 5–6

18 Naidech AM, Drescher J, Tamul P, Shaibani A, Batjer HH, Alberts MJ. Acute physiological derangement is associated with early radiographic cerebral infarction after subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatr* 2006; **77**: 1340–4

19 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

20 Minhas PS, Menon DK, Smielewski P, *et al.* Positron emission tomographic cerebral perfusion disturbances and transcranial Doppler findings among patients with neurological deterioration after subarachnoid hemorrhage. *Neurosurgery* 2003; **52**: 1017–24

21 Petruk KC, West M, Mohr G, *et al.* Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. *J Neurosurg* 1988; **68**: 505–17

22 Feigin VL, Rinkel GJ, Algra A, Vermeulen M, van Gijn J. Calcium antagonists in patients with aneurysmal subarachnoid hemorrhage: a systematic review. *Neurology* 1998; **50**: 876–83

23 Macdonald RL, Kassell NF, Mayer S, *et al.* Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke* 2008; **39**: 3015–21

24 Polin RS, Coenen VA, Hansen CA, *et al.* Efficacy of transluminal angioplasty for the management of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2000; **92**: 284–90

25 Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. *Stroke* 1994; **25**: 1342–7

26 Kusaka G, Ishikawa M, Nanda A, Granger DN, Zhang JH. Signaling pathways for early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 2004; **24**: 916–25

27 Swift DM, Solomon RA. Subarachnoid hemorrhage fails to produce vasculopathy or chronic blood flow changes in rats. *Stroke* 1988; **19**: 878–82

28 Aoki T, Nishimura M. The development and the use of experimental animal models to study the underlying mechanisms of CA formation. *J Biomed Biotechnol* 2011; **2011**: 1–10

29 Sobey CG. Cerebrovascular dysfunction after subarachnoid haemorrhage: novel mechanisms and directions for therapy. *Clin Exp Pharmacol Physiol* 2001; **28**: 926–9

30 Nornes H. The role of intracranial pressure in the arrest of hemorrhage in patients with ruptured intracranial aneurysm. *J Neurosurg* 1973; **39**: 226–34

31 Grote E, Hassler W. The critical first minutes after subarachnoid hemorrhage. *Neurosurgery* 1988; **22**: 654

32 Bederson JB, Germano IM, Guarino L. Cortical blood flow and cerebral perfusion pressure in a new non-craniotomy model

of subarachnoid hemorrhage in the rat. *Stroke* 1995; **26**: 1086–91
33 Nornes H, Magnaes B. Intracranial pressure in patients with ruptured saccular aneurysm. *J Neurosurg* 1972; **36**: 537–47
34 Asano T, Sano K. Pathogenetic role of no-reflow phenomenon in experimental subarachnoid hemorrhage in dogs. *J Neurosurg* 1977; **46**: 454–66
35 Schwartz AY, Masago A, Sehba FA, Bederson JB. Experimental models of subarachnoid hemorrhage in the rat: a refinement of the endovascular filament model. *J Neurosci Methods* 2000; **96**: 161–7
36 Claassen J, Carhuapoma J, Kreiter K, Du E, Connolly E, Mayer S. Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. *Stroke* 2002; **33**: 1225
37 Keep RF, Andjelkovic AV, Stamatovic SM, Shakui P, Ennis SR. Ischemia-induced endothelial cell dysfunction. *Acta Neurochir Suppl* 2005; **95**: 399–402
38 Rätsep T, Asser T. Cerebral hemodynamic impairment after aneurysmal subarachnoid hemorrhage as evaluated using transcranial Doppler ultrasonography: relationship to delayed cerebral ischemia and clinical outcome. *J Neurosurg* 2001; **95**: 393–401
39 Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. *Crit Care Med* 2001; **29**: 158–63
40 Aries MJH, Elting JW, De Keyser J, Kremer BPH, Vroomen PCAJ. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke* 2010; **41**: 2697–704
41 Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; **2**: 161–92
42 Ayer R, Zhang J. Connecting the early brain injury of aneurysmal subarachnoid hemorrhage to clinical practice. *Turk Neurosurg* 2010; **20**: 159–66
43 Osuka K, Suzuki Y, Tanazawa T, *et al.* Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. *Acta Neurochir* 1998; **140**: 943–51
44 Mathiesen T, Edner G, Ulfarsson E, Andersson B. Cerebrospinal fluid interleukin-1 receptor antagonist and tumor necrosis factor-alpha following subarachnoid hemorrhage. *J Neurosurg* 1997; **87**: 215–20
45 Leao A. Spreading depression of activity in the cerebral cortex. *J Neurophysiol* 1944; **7**: 359
46 Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain* 1994; **117** (Pt 1): 199–210
47 Dohmen C, Sakowitz OW, Fabricius M, *et al.* Spreading depolarizations occur in human ischemic stroke with high incidence. *Ann Neurol* 2008; **63**: 720–8
48 Strong AJ, Fabricius M, Boutelle MG, *et al.* Spreading and synchronous depressions of cortical activity in acutely injured human brain. *Stroke* 2002; **33**: 2738–43
49 Dreier JP, Major S, Manning A, *et al.* Cortical spreading ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid haemorrhage. *Brain* 2009; **132** (Pt 7): 1866–81
50 Leao A. Pial circulation and spreading depression of activity in the cerebral cortex. *J Neurophysiol* 1944; **7**: 391–6
51 Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab* 2011; **31**: 17–35
52 Lauritzen M. Long-lasting reduction of cortical blood flow of the brain after spreading depression with preserved autoregulation and impaired CO_2 response. *J Cereb Blood Flow Metab* 1984; **4**: 546–54
53 Dreier JP, Woitzik J, Fabricius M, *et al.* Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations. *Brain* 2006; **129** (Pt 12): 3224–37
54 Shin HK, Dunn AK, Jones PB, Boas DA, Moskowitz MA, Ayata C. Vasoconstrictive neurovascular coupling during focal ischemic depolarizations. *J Cereb Blood Flow Metab* 2006; **26**: 1018–30
55 Bosche B, Graf R, Ernestus R-I, *et al.* Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. *Ann Neurol* 2010; **67**: 607–17
56 Woitzik J, Dreier JP, Hecht N, *et al.* Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 2012; **32**: 203–12
57 Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A. Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. *Neurochem Res* 1997; **22**: 1249–55
58 Frijns CJM, Fijnheer R, Algra A, van Mourik JA, van Gijn J, Rinkel GJE. Early circulating levels of endothelial cell activation markers in aneurysmal subarachnoid haemorrhage: associations with cerebral ischaemic events and outcome. *J Neurol Neurosurg Psychiatr* 2006; **77**: 77–83
59 Hirashima Y, Nakamura S, Suzuki M, *et al.* Cerebrospinal fluid tissue factor and thrombin–antithrombin III complex as indicators of tissue injury after subarachnoid hemorrhage. *Stroke* 1997; **28**: 1666–70
60 Ikeda K, Asakura H, Futami K, Yamashita J. Coagulative and fibrinolytic activation in cerebrospinal fluid and plasma after subarachnoid hemorrhage. *Neurosurgery* 1997; **41**: 344–9
61 Peltonen S, Juvela S, Kaste M, Lassila R. Hemostasis and fibrinolysis activation after subarachnoid hemorrhage. *J Neurosurg* 1997; **87**: 207–14
62 Romano JG, Forteza AM, Concha M, *et al.* Detection of microemboli by transcranial Doppler ultrasonography in aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2002; **50**: 1026–30; discussion 1030–1
63 Suzuki S, Kimura M, Souma M, Ohkima H, Shimizu T, Iwabuchi T. Cerebral microthrombosis in symptomatic cerebral vasospasm—a quantitative histological study in autopsy cases. *Neurol Med Chir (Tokyo)* 1990; **30**: 309–16
64 Stein SC, Browne KD, Chen X-H, Smith DH, Graham DI. Thromboembolism and delayed cerebral ischemia after subarachnoid hemorrhage: an autopsy study. *Neurosurgery* 2006; **59**: 781–7
65 Neil-Dwyer G, Lang DA, Doshi B, Gerber CJ, Smith PW. Delayed cerebral ischaemia: the pathological substrate. *Acta Neurochir* 1994; **131**: 137–45
66 Vernieri F, Pasqualetti P, Matteis M, *et al.* Effect of collateral blood flow and cerebral vasomotor reactivity on the outcome of carotid artery occlusion. *Stroke* 2001; **32**: 1552–8
67 Romero JR, Pikula A, Nguyen TN, Nien YL, Norbash A, Babikian VL. Cerebral collateral circulation in carotid artery disease. *Curr Cardiol Rev* 2009; **5**: 279–88
68 Liebeskind D. Collateral circulation. *Stroke* 2003; **34**: 2279–84
69 Toni D, Fiorelli M, Bastianello S, *et al.* Acute ischemic strokes improving during the first 48 hours of onset: predictability,

outcome, and possible mechanisms. A comparison with early deteriorating strokes. *Stroke* 1997; **28**: 10–4

70 Bang OY, Saver JL, Buck BH, *et al.* Impact of collateral flow on tissue fate in acute ischaemic stroke. *J Neurol Neurosurg Psychiatr* 2008; **79**: 625–9

71 Bang OY, Saver JL, Alger JR, *et al.* Determinants of the distribution and severity of hypoperfusion in patients with ischemic stroke. *Neurology* 2008; **71**: 1804–11

72 Shaw MD, Vermeulen M, Murray GD, Pickard JD, Bell BA, Teasdale GM. Efficacy and safety of the endothelin, receptor antagonist TAK-044 in treating subarachnoid hemorrhage: a report by the Steering Committee on behalf of the UK/Netherlands/Eire TAK-044 Subarachnoid Haemorrhage Study Group. *J Neurosurg* 2000; **93**: 992–7

73 Vajkoczy P, Meyer B, Weidauer S, *et al.* Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: results of a randomized, double-blind, placebo-controlled, multicenter phase IIa study. *J Neurosurg* 2005; **103**: 9–17

74 Barth M, Capelle H-H, Münch E, *et al.* Effects of the selective endothelin A (ET(A)) receptor antagonist clazosentan on cerebral perfusion and cerebral oxygenation following severe subarachnoid hemorrhage—preliminary results from a randomized clinical series. *Acta Neurochir* 2007; **149**: 911–8

75 Actelion website. Available from http://www.actelion.com/en/our-company/news-and-events/index.page?newsId=1446888. Last accessed 18 May 2011

76 Clinicaltrials.gov website. Available from http://clinicaltrials.gov/ct2/show/study/NCT00940095?term=Vasospasm&rank=14#locn. Last accessed 18 May 2011

77 Wong GKC, Poon WS. Clazosentan for patients with subarachnoid haemorrhage: lessons learned. *Lancet Neurol* 2011; **10**: 871

78 Chen G, Tariq A, Ai J, *et al.* Different effects of clazosentan on consequences of subarachnoid hemorrhage in rats. *Brain Res* 2011; **1392**: 132–9

79 Peroutka SJ, Allen GS. Calcium channel antagonist binding sites labeled by 3H-nimodipine in human brain. *J Neurosurg* 1983; **59**: 933–7

80 Cheung JY, Bonventre JV, Malis CD, Leaf A. Calcium and ischemic injury. *N Engl J Med* 1986; **314**: 1670–6

81 Kazda S, Towart R. Nimodipine: a new calcium antagonistic drug with a preferential cerebrovascular action. *Acta Neurochir* 1982; **63**: 259–65

82 Pickard JD, Murray GD, Illingworth R, *et al.* Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *Br Med J* 1989; **298**: 636–42

83 Dorhout Mees SM, Rinkel GJE, Feigin VL, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2007; CD000277

84 Pisani A, Calabresi P, Tozzi A, D'Angelo V, Bernardi G. L-type Ca^{2+} channel blockers attenuate electrical changes and Ca^{2+} rise induced by oxygen/glucose deprivation in cortical neurons. *Stroke* 1998; **29**: 196–201; discussion 202

85 Horn J, Limburg M. Calcium antagonists for ischemic stroke: a systematic review. *Stroke* 2001; **32**: 570–6

86 Langham J, Goldfrad C, Teasdale G, Shaw D, Rowan K. Calcium channel blockers for acute traumatic brain injury. *Cochrane Database Syst Rev* 2003; CD000565

87 Vergouwen MDI, Vermeulen M, de Haan RJ, Levi M, Roos YBWEM. Dihydropyridine calcium antagonists increase fibrinolytic activity: a systematic review. *J Cereb Blood Flow Metab* 2006; **27**: 1293–308

88 Dreier JP, Windmüller O, Petzold G, Lindauer U, Einhäupl KM, Dirnagl U. Ischemia triggered by red blood cell products in the subarachnoid space is inhibited by nimodipine administration or moderate volume expansion/hemodilution in rats. *Neurosurgery* 2002; **51**: 1457–65

89 Denny-Brown D. The treatment of recurrent cerebrovascular symptoms and the question of 'vasospasm'. *Med Clin North Am* 1951; **35**: 1457–74

90 Kosnik EJ, Hunt WE. Postoperative hypertension in the management of patients with intracranial arterial aneurysms. *J Neurosurg* 1976; **45**: 148–54

91 Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP. Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. *Neurosurgery* 1982; **11**: 337–43

92 Rinkel GJE, Feigin VL, Algra A, van Gijn J. Circulatory volume expansion therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2004; CD000483

93 Dankbaar JW, Slooter AJ, Rinkel GJ, Schaaf ICVD. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review. *Crit Care* 2010; **14**: R23

94 van den Bergh WM, Algra A, van der Sprenkel JWB, Tulleken CAF, Rinkel GJE. Hypomagnesemia after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2003; **52**: 276–81

95 van den Bergh WM, Zuur JK, Kamerling NA, *et al.* Role of magnesium in the reduction of ischemic depolarization and lesion volume after experimental subarachnoid hemorrhage. *J Neurosurg* 2002; **97**: 416–22

96 van der Hel WS, van den Bergh WM, Nicolay K, Tulleken KA, Dijkhuizen RM. Suppression of cortical spreading depressions after magnesium treatment in the rat. *Neuroreport* 1998; **9**: 2179–82

97 Wong GKC, Poon WS, Chan MTV, *et al.* Plasma magnesium concentrations and clinical outcomes in aneurysmal subarachnoid hemorrhage patients: post hoc analysis of intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage trial. *Stroke* 2010; **41**: 1841–4

98 Wong GK, Boet R, Poon WS, *et al.* Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage: an updated systemic review and meta-analysis. *Crit Care* 2011; **15**: R52

99 Peters SAE, Palmer MK, Grobbee DE, *et al.* C-reactive protein lowering with rosuvastatin in the METEOR study. *J Intern Med* 2010; **268**: 155–61

100 Ota H, Eto M, Kano MR, *et al.* Induction of endothelial nitric oxide synthase, sirt1, and catalase by statins inhibits endothelial senescence through the Akt pathway. *Arterioscler Thromb Vasc Biol* 2010; **30**: 2205–11

101 Szapary L, Horvath B, Marton Z, *et al.* Short-term effect of low-dose atorvastatin on haemorrheological parameters, platelet aggregation and endothelial function in patients with cerebrovascular disease and hyperlipidaemia. *CNS Drugs* 2004; **18**: 165–72

102 Cheng G, Wei L, Zhi-Dan S, Shi-Guang Z, Xiang-Zhen L. Atorvastatin ameliorates cerebral vasospasm and early brain injury after subarachnoid hemorrhage and inhibits caspase-dependent apoptosis pathway. *BMC Neurosci* 2009; **10**: 7

103 Merlo L, Cimino F, Scibilia A, *et al.* Simvastatin administration ameliorates neurobehavioral consequences of subarachnoid hemorrhage in the rat. *J Neurotrauma* 2011; **28**: 2493–501

104 Lynch JR, Wang H, Mcgirt MJ, *et al.* Simvastatin reduces vasospasm after aneurysmal subarachnoid hemorrhage: results of a pilot randomized clinical trial. *Stroke* 2005; **36**: 2024–6

105 Chou SH-Y, Smith EE, Badjatia N, *et al.* A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage. *Stroke* 2008; **39**: 2891–3

106 Vergouwen M, Meijers J, Geskus R, *et al.* Biologic effects of simvastatin in patients with aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled randomized trial. *J Cereb Blood Flow Metab* 2009; **29**: 1444–53

107 Tseng M-Y, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase II randomized placebo-controlled trial. *Stroke* 2005; **36**: 1627–32

108 Vergouwen MDI, de Haan RJ, Vermeulen M, Roos YBWEM. Effect of statin treatment on vasospasm, delayed cerebral ischemia, and functional outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis update. *Stroke* 2010; **41**: e47–52

109 Chang C-Z, Wu S-C, Lin C-L, Hwang S-L, Howng S-L, Kwan A-L. Atorvastatin preconditioning attenuates the production of endothelin-1 and prevents experimental vasospasm in rats. *Acta Neurochir* 2010; **152**: 1399–406

110 Parra A, Kreiter KT, Williams S, *et al.* Effect of prior statin use on functional outcome and delayed vasospasm after acute aneurysmal subarachnoid hemorrhage: a matched controlled cohort study. *Neurosurgery* 2005; **56**: 476–84

111 Mcgirt MJ, Blessing R, Alexander MJ, *et al.* Risk of cerebral vasopasm after subarachnoid hemorrhage reduced by statin therapy: A multivariate analysis of an institutional experience. *J Neurosurg* 2006; **105**: 671–4

112 Moskowitz SI, Ahrens C, Provencio JJ, Chow M, Rasmussen PA. Prehemorrhage statin use and the risk of vasospasm after aneurysmal subarachnoid hemorrhage. *Surg Neurol* 2009; **71**: 311–7

113 Singhal AB, Topcuoglu MA, Dorer DJ, Ogilvy CS, Carter BS, Koroshetz WJ. SSRI and statin use increases the risk for vasospasm after subarachnoid hemorrhage. *Neurology* 2005; **64**: 1008–13

114 STASH Trial Website. Available from http://www.stashtrial.com/home.html. Last accessed 4 June 2011.

115 van den Bergh WM, MASH Study Group, Algra A, *et al.* Randomized controlled trial of acetylsalicylic acid in aneurysmal subarachnoid hemorrhage: the MASH Study. *Stroke* 2006; **37**: 2326–30

116 Dorhout Mees SM, van den Bergh WM, Algra A, Rinkel GJE. Antiplatelet therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2007; CD006184

117 Libersan D, Khalil A, Dagenais P, *et al.* The low molecular weight heparin, enoxaparin, limits infarct size at reperfusion in the dog. *Cardiovasc Res* 1998; **37**: 656–66

118 Gikakis N, Khan MM, Hiramatsu Y, *et al.* Effect of factor Xa inhibitors on thrombin formation and complement and neutrophil activation during in vitro extracorporeal circulation. *Circulation* 1996; **94** (9 Suppl.): II341–6

119 Xi G, Wagner KR, Keep RF, *et al.* Role of blood clot formation on early edema development after experimental intracerebral hemorrhage. *Stroke* 1998; **29**: 2580–6

120 Jonas S, Sugimori M, Llinás R. Is low molecular weight heparin a neuroprotectant? *Ann N Y Acad Sci* 1997; **825**: 389–93

121 Siironen J, Juvela S, Varis J, *et al.* No effect of enoxaparin on outcome of aneurysmal subarachnoid hemorrhage: a randomized, double-blind, placebo-controlled clinical trial. *J Neurosurg* 2003; **99**: 953–9

122 Wurm G, Tomancok B, Nussbaumer K, Adelwöhrer C, Holl K. Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: a double-blind, randomized comparison of enoxaparin versus placebo. *Clin Neurol Neurosurg* 2004; **106**: 97–103

123 Roos YB, Rinkel GJ, Vermeulen M, Algra A, van Gijn J. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2000; CD001245

124 Amin-Hanjani S, Ogilvy CS, Barker FG II. Does intracisternal thrombolysis prevent vasospasm after aneurysmal subarachnoid hemorrhage? A meta-analysis. *Neurosurgery* 2004; **54**: 326–35

125 Starke RM, Kim GH, Komotar RJ, *et al.* Endothelial nitric oxide synthase gene single-nucleotide polymorphism predicts cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 2008; **28**: 1204–11

126 Khurana VG, Meissner I, Meyer FB. Update on genetic evidence for rupture-prone compared with rupture-resistant intracranial saccular aneurysms. *Neurosurg Focus* 2004; **17**: E7

127 Ko NU, Rajendran P, Kim H, *et al.* Endothelial nitric oxide synthase polymorphism (-786T->C) and increased risk of angiographic vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke* 2008; **39**: 1103–8

128 Corder EH, Nicoll JA, Murray G, *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; **261**: 921–3

129 Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet* 1997; **350**: 1069–71

130 Alberts MJ, Graffagnino C, Khurana VG, *et al.* ApoE genotype and survival from intracerebral haemorrhage. *Lancet* 1995; **346**: 575

131 McCarron MO, Muir KW, Nicoll JA, *et al.* Prospective study of apolipoprotein E genotype and functional outcome following ischemic stroke. *Arch Neurol* 2000; **57**: 1480–4

132 Gao J, Wang H, Sheng H, *et al.* A novel apoE-derived therapeutic reduces vasospasm and improves outcome in a murine model of subarachnoid hemorrhage. *Neurocrit Care* 2006; **4**: 25–31

133 Niskakangas T, Ohman J, Niemela M, Ilveskoski E, Kunnas TA, Karhunen PJ. Association of apolipoprotein E polymorphism with outcome after aneurysmal subarachnoid hemorrhage: a preliminary study. *Stroke* 2001; **32**: 1181–4

134 Lanterna LA, Ruigrok Y, Alexander S, *et al.* Meta-analysis of APOE genotype and subarachnoid hemorrhage: clinical outcome and delayed ischemia. *Neurology* 2007; **69**: 766–75

135 Juvela S, Siironen J, Lappalainen J. Apolipoprotein E genotype and outcome after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2009; **110**: 989–95

136 Miyata M, Smith JD. Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and beta-amyloid peptides. *Nat Genet* 1996; **14**: 55–61

137 Pepe MG, Curtiss LK. Apolipoprotein E is a biologically active constituent of the normal immunoregulatory lipoprotein, LDL-In. *J Immunol* 1986; **136**: 3716–23

138 Piper RD, Lambert GA. Inhalational anesthetics inhibit spreading depression: relevance to migraine. *Cephalalgia* 1996; **16**: 87–92

139 Kudo C, Nozari A, Moskowitz MA, Ayata C. The impact of anesthetics and hyperoxia on cortical spreading depression. *Exp Neurol* 2008; **212**: 201–6

140 Kitahara Y, Taga K, Abe H, Shimoji K. The effects of anesthetics on cortical spreading depression elicitation and c-fos expression in rats. *J Neurosurg Anesthesiol* 2001; **13**: 26–32

141 Thomson H, Harper NJ, Parkes A. Use of the AnaConDa anaesthetic delivery system to treat life-threatening asthma. *Anaesthesia* 2007; **62**: 295–6

142 Wentlandt K, Samoilova M, Carlen PL, Beheiry El H. General anesthetics inhibit gap junction communication in cultured organotypic hippocampal slices. *Anesth Analg* 2006; **102**: 1692–8

143 Sasaki R, Hirota K, Asahi T, Yamazaki M. The effects of thiopental on spreading depression induced by anoxia in the rat hippocampal slice in vitro. *Hiroshima J Anaesth* 2002; **38**: 211–4

144 Hernández-Cáceres J, Macias-González R, Brozek G, Bures J. Systemic ketamine blocks cortical spreading depression but does not delay the onset of terminal anoxic depolarization in rats. *Brain Res* 1987; **437**: 360–4

145 Sakowitz OW, Unterberg AW. Detecting and treating microvascular ischemia after subarachnoid hemorrhage. *Curr Opin Crit Care* 2006; **12**: 103–11

146 Petzold A, Keir G, Kay A, Kerr M, Thompson EJ. Axonal damage and outcome in subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatr* 2006; **77**: 753–9

147 Fountas KN, Tasiou A, Kapsalaki EZ, *et al.* Serum and cerebrospinal fluid C-reactive protein levels as predictors of vasospasm in aneurysmal subarachnoid hemorrhage. Clinical article. *Neurosurg Focus* 2009; **26**: E22

148 Sehba FA, Pluta RM, Zhang JH. Metamorphosis of subarachnoid hemorrhage research: from delayed vasospasm to early brain injury. *Mol Neurobiol* 2011; **43**: 27–40

149 Dreier JP, Körner K, Ebert, *et al.* Nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K+ is increased in the subarachnoid space. *J Cereb Blood Flow Metab* 1998; **18**: 978–90