Review Articles

Haemodynamic considerations in the management of patients with subarachnoid haemorrhage

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Cerebral vasospasm occurs, following subarachnoid haemorrhage, in the majority of patients and is accompanied by cerebral ischaemia in 30%. The objectives of this article are to review (1) the effects of subarachnoid haemorrhage and vasospasm on cerebral blood flow(CBF); (2) the effects of induced hypotension and hypocapnia on CBF in these patients; (3) current therapy for cerebral ischaemia from vasospasm. The medical literature was searched using Index Medicus; for the period 1983–90 this search was done on a computer with the CD-ROM version of Index Medicus, Silver Platter®. Papers were selected on the basis of validity and applicability to clinical practice; animal studies are included when human data is lacking. Cerebral vasospasm may decrease cerebral blood flow, disturb autoregulation and place the patient at risk for delayed cerebral ischaemia. Intraoperative induced hypotension and hypocapnia can decrease CBF further, although effects of either on outcome have not been evaluated. Calcium antagonists are effective for both the prevention and the treatment of delayed cerebral ischaemia. Of the mechanical treatments, systemic-arterial hypertension has the firmest scientific foundation, although this is frequently combined with haemodilution and blood volume expansion. There is a need for randomized clinical trials to assess the efficacy of these latter treatments.

L'hémorragie subarachnoïdienne s'accompagne souvent d'un vasospasme, ce qui provoque une ischémie cérébrale dans 30% des cas. Cet article fait le point 1) sur les effets d'une hémorragie subarachnoïdienne et du vasospasme sur le débit sanguin cérébral (CBF), 2) sur les effets de l'hypotension délibérée et de l'hypocapnie sur le CBF chez ces malades, et 3) sur le traitement de l'ischémie cérébrale provoquée par un vasospasme. Les articles pertinents ont été repérés à l'aide de l'Index Medicus. Pour les années 1983–1990, nous vons utilisé Silver Platter®, la version informatisée CD-ROM de l'Index Medicus. On a retenu les articles pertinents, applicables à la pratique clinique et on a inclus les études expérimentales chez les animaux lorsque l'on ne possédait pas de données chez les humains. Le vasospasme peut diminuer le débit sanguin cérébral et déranger les mécanismes d'autorégulation. Le sujet risque donc une ischémie cérébrale. Durant l'anesthésie, l'hypotension et l'hypocapnie délibérées peuvent réduire le CBF, mais on ne connait pas les effets de ces interventions sur les résultats. On peut prévenir et traiter l'ischémie cérébrale due au vasospasme à l'aide d'antagonistes du calcium. Parmi les traitements hémodynamiques, celui qui s'appuie le plus sur des fondements scientifiques sûrs est l'hypertension artérielle. Toutefois, on l'utilise souvent en conjonction avec l'hémodilution et l'augmentation du volume circulant. On manque d'études cliniques à double insu pour l'évaluation de ces traitements.

Key words
BRAIN: blood flow, metabolism, ischaemia, subarachnoid haemorrhage, vasospasm;
PHARMACOLOGY: calcium antagonists;
SURGERY: neurologic.

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Contents

- Aetiology and pathogenesis
- Measurement of cerebral blood flow
  - Time course of vasospasm
- Induced hypotension and hyperventilation
  - Autoregulation
  - CO_2 reactivity

Therapy for cerebral vasospasm
- Calcium antagonists
  - Prevention of delayed cerebral ischaemia
  - Treatment of delayed cerebral ischaemia
  - Implications for anaesthetic management
- Haemodilution
- Systemic arterial hypertension
- Blood volume expansion
- Complications of therapy
- Guidelines for volume expansion

Conclusions

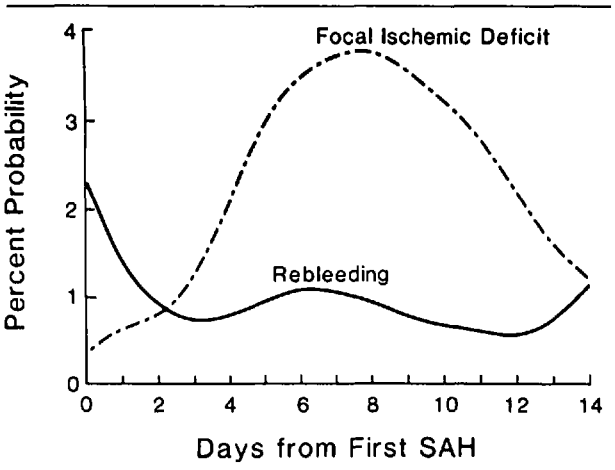

FIGURE 1 Percentage probability of focal ischaemic deficit (caused by symptomatic vasospasm) and rebleeding during the first 14 days after subarachnoid haemorrhage. Reproduced with permission from Kassell NF *et al.*[74]

The focus of anaesthetic and intensive care management of patients with aneurysmal subarachnoid haemorrhage has, over the past 15 yr, shifted from medical management to prevent rebleeding to early operation to secure the aneurysm combined with measures to prevent or treat cerebral ischaemia from vasospasm.[1] The two principal risks to the patients who survive a subarachnoid haemorrhage are rebleeding and delayed cerebral ischaemia related to cerebral vasospasm. It has been estimated[1] that of those patients who survive the initial haemorrhage and reach a neurosurgical centre, 6% will die from rebleeding before the aneurysm can be clipped, while 7% will die from vasospasm. Rebleeding and vasospasm also account for major neurological morbidity, occurring, respectively, in 1% and 7% of patients following subarachnoid haemorrhage. To reduce the risk of rebleeding, a recent trend in neurosurgery has favoured early operation, attempting to secure the aneurysm in the first 48–72 hr post-ictus before vasospasm becomes a frequent clinical problem (Figure 1) rather than waiting 14 days for the risk of vasospasm to subside.

Since cerebral vasospasm may be present without clinical evidence of ischaemia, early timing of aneurysm clipping may increase the chance that anaesthesia and surgery are performed in patients who are at risk for delayed cerebral ischaemia. Delayed cerebral ischaemia therefore remains a major problem before and after successful aneurysm clipping and is an important factor contributing to the less than 50% full recovery rate of patients initially considered to have a relatively good prognosis based on their neurological grade at admission to hospital (Table I).[2]

First, the pathophysiological consequences of subarachnoid haemorrhage on intracranial pressure, fluid and electrolyte balance, cerebral metabolism and cerebral blood flow and volume will be reviewed before discussion of the diagnosis and management of delayed cerebral ischaemia.

Pathophysiology

Intracranial pressure

Rupture of a cerebral aneurysm with subsequent arterial bleeding may cause dramatic changes in intracranial pressure.[3] The rupture of the aneurysm and filling of the subarachnoid and intraventricular spaces with extravasated blood produces an acute increase in intracranial pressure (ICP) (Figure 2), which may play a role in the arrest of the bleeding.[4] In severe haemorrhage, cerebral perfusion pressure (mean arterial pressure – the greater of ICP or intracranial venous pressure) may decrease to low levels (10–30 mmHg) with a concomitant decrease in cerebral blood flow.[3] Arterioles dilate in response to the acute rise in ICP.[5] At ICP values which approach mean arterial pressure (Figure 2, B and C), a pressor response ensues.[3] If severe, these events can lead to brain herniation and death.

Subacutely, subarachnoid haemorrhage may be complicated by intracranial hypertension from hydrocephalus. Although the site of obstruction of the CSF circulation by blood or blood products has not been established, the most likely candidates include the ventricles, the outlet to the fourth ventricle and diffuse layering of blood in the subarachnoid space.[6] Following subarachnoid haemorrhage, dilated ventricles are observed on the computed tomographic (CT) scan obtained at admission in 15% of patients and a further 9% of patients develop

TABLE I Classification of neurological condition following subarachnoid haemorrhage[2,11]

Grade	*Condition*	*Probability of Survival (%)*
0	Unruptured aneurysm	n/a
I	Asymptomatic, of minimal headache and slight nuchal rigidity	90
II	Moderate to severe headache, nuchal rigidity, no neurological deficits other than cranial nerve palsy	75
III	Drowsiness, confusion or mild focal deficit	65
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity	45
V	Deep coma, decerebrate rigidity, moribund appearance	5
All grades		65

symptoms consistent with hydrocephalus.[6] The patient group at risk can be identified by the factors which have been found[6] to occur in association with clinically important hydrocephalus. Factors most predictive of clinical hydrocephalus are: advanced age, pre-subarachnoid haemorrhage hypertension, admission blood pressure, computed tomography (CT) findings of hydrocephalus or intraventricular haemorrhage. Postoperative blood pressure after aneurysm surgery greater than 150/90 mmHg, subarachnoid blood on CT scan and location of the aneurysm in the posterior cerebral circulation were less important predictors. Although the indications for CSF drainage are somewhat controversial, the ICP, the severity of haemorrhage and the presence of intraventricular blood have been suggested as important factors to consider.[7] Many of these features are demonstrated in Figure 3.

Cerebral function

Cerebral metabolism as reflected in the metabolic rate for oxygen ($CMRO_2$), and cerebral blood flow (CBF) are reduced by subarachnoid haemorrhage, even in neurologically intact patients without vasospasm.[8,9] This appears to be due to a direct toxic effect of subarachnoid blood on brain metabolism.[8,9]

In addition to these diffuse mechanical, haemodynamic and metabolic effects, the rupture of an aneurysm can cause focal neurological deficits when the jet of blood is directed into the brain, producing an intracerebral haematoma with destruction of brain and a local mass effect (Figure 3). These events and disturbances in cerebral function determine the patient's clinical status in the immediate post-haemorrhage period. Neurological status following subarachnoid haemorrhage has been formalized into classification systems such as that of Hunt and Hess[2] (Table I) or Botterell.[10] The probability of survival

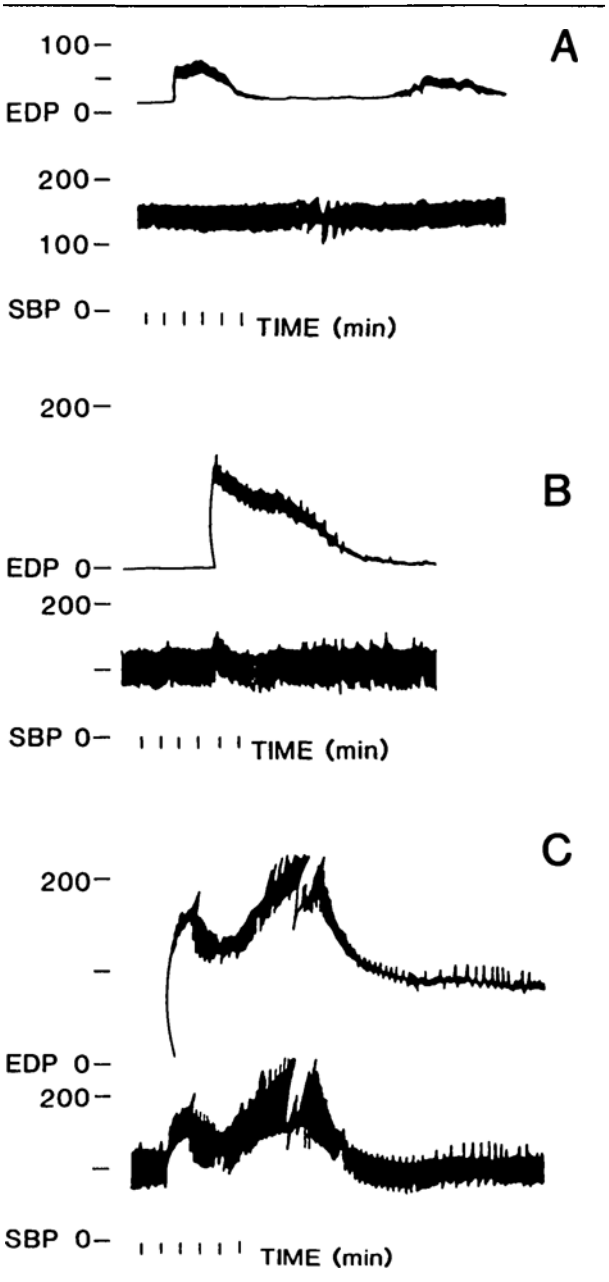

FIGURE 2 Effects of experimental subarachnoid haemorrhage on extradural pressure (EDP) and systemic blood pressure (SBP) in mild (A), moderate (B), and severe (C) subarachnoid haemorrhage. Figure reproduced from Dorsch *et al.*[3] with permission.

for each of the grades of the Hunt and Hess system has been determined.[11] Note that in Table I, there has been an important abbreviation of the survival data. The survival probabilities shown refer to the summary of results from clinical grades measured at several times after the haemorrhage. As shown by Alvord *et al.*,[11] survival rates in any of the clinical grades increase with the interval between the initial haemorrhage and the time that the

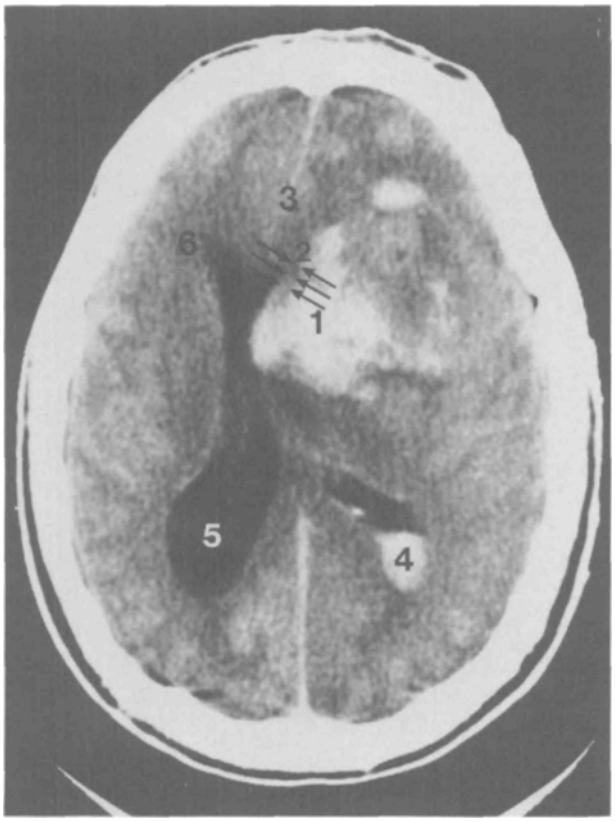

FIGURE 3 Computed tomography scan of the head of a patient following subarachnoid haemorrhage from a middle cerebral artery aneurysm. Note the presence of an intracerebral haematoma on the right (1) with mass effect indicated by the obliteration of the anterior right lateral ventricle (2 with arrows) and midline shift (3). A ventricular "cast" of blood is present in the posterior horn of the right lateral ventricle (4) and dilatation of the left lateral ventricle (5) with hypodensity in the periventricular tissue surrounding the anterior horn (6) suggest the presence of acute hydrocephalus.

clinical grade is determined. For example, a patient graded 1 on the first day after the haemorrhage has a 65% chance of survival, while a patient graded 1 twenty-one days later has a 95% chance of surviving.

Blood volume, fluid and electrolyte balance

Many patients have alterations in blood volume and in sodium and water metabolism following subarachnoid haemorrhage.[12] Decreases in red cell volume and total circulating blood volume have been demonstrated.[13,14] A decrease in plasma volume greater than 10% has been observed in approximately 50% of patients following SAH.[15] In the latter study, a negative sodium balance was associated with the decreased plasma volume in 10/11 patients. These changes may reflect contraction of the extracellular fluid (ECF) volume due to a salt and water deficiency[14] caused by sodium loss in the urine.[14,16]

The cause of the natriuresis in the patients with negative sodium balance is not clear. Supine diuresis[17] during enforced bed rest may be a factor. Atrial natriuretic factor (ANF) levels are elevated in patients with subarachnoid haemorrhage[18,19] and may contribute to the natriuresis. Antidiuretic hormone (ADH) levels are also high in patients following subarachnoid haemorrhage, both in absolute terms and in relation to the serum osmolarity.[19] Contraction of intravascular volume is common in these patients and ADH secretion may be triggered by the low-pressure receptors in the atria, which respond to decreases in atrial volume by decreasing their inhibitory effect on ADH release.[20] The presence of elevated levels of atrial natriuretic factor would appear to be inappropriate in these patients – this protein is usually released from the cardiocytes of the atria in response to atrial stretch during isotonic or hypertonic volume loading, the reverse situation to that found in patients following subarachnoid haemorrhage. The elevated ANF levels may be explained by the observation that ADH has been shown to stimulate atrial natriuretic factor release.[21]

Hyponatraemia is the most frequent electrolyte disturbance observed in patients following subarachnoid haemorrhage, occurring in 4–25% of patients.[6,22] As outlined above, there is good evidence for decreased circulating volume and increased urinary sodium loss in some patients with SAH. It may therefore not be appropriate to assume that hyponatraemic patients have a normal total body sodium and that the hyponatraemia reflects the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The clinician should carefully evaluate the patient's extracellular fluid volume status to determine whether it is normal or contracted. Hypovolaemia should be suspected in patients with recent weight loss, tachycardia, orthostatic hypotension and decreased central venous pressure. In normovolaemic patients with SIADH, the urine is concentrated and usually has a sodium concentration of more than 20 $mEq \cdot L^{-1}$.[23] The high urinary sodium concentration reflects the fact that the daily positive sodium balance must be excreted in a very small volume of urine. In patients with SIADH and sodium restriction or volume contraction, urinary sodium concentrations are appropriately low, and renal sodium loss is not a likely cause of the negative sodium balance or hypovolaemia.[23]

It is important to distinguish, by clinical evaluation of extracellular volume, the patients with hyponatraemia on the basis of a total body deficit of sodium and a lesser deficit of water from patients with an excess of total body water due to ADH release in response to surgery, nausea, haemorrhage and other perioperative factors.[24] Treatment for hyponatraemia in patients with ECF volume contraction is based on restoration of ECF volume, while water

excess is treated by water restriction. The correction of hypovolaemia is particularly important since volume contraction has been shown to be associated with increased risk of cerebral ischaemia from vasospasm, as will be discussed below. A preliminary report[25] suggested that fluid administration in patients with subarachnoid haemorrhage (2.5–3.5 $L \cdot day^{-1}$ normal saline, increased to 6–8 $L \cdot day^{-1}$ after aneurysm clipping) maintained plasma volume and decreased serum concentrations of ADH, aldosterone and plasma renin. Atrial natriuretic factor concentrations were increased.

Delayed ischaemia from cerebral vasospasm

Clinical presentation

Delayed cerebral ischaemia is recognized by the development of a focal neurological deficit or depression of level of consciousness three to nine days following a subarachnoid haemorrhage in patients in whom other causes of neurological deterioration, such as rebleeding, hydrocephalus, intracranial haematoma, and metabolic disturbances (e.g., hyponatraemia) have been excluded. The clinical presentation is characterized by disorientation and drowsiness which evolve over a period of hours and which may precede the appearance of focal deficits.

Etiology and pathogenesis

The cause(s) of the vascular spasm seen in the large cerebral vessels following subarachnoid haemorrhage has not been identified despite intense research efforts for the past 20 yr.

The hypotheses concerning the pathogenesis of cerebral vasospasm can be grouped into three major categories:[1]

1 Contraction or failure of vasodilatation of cerebral arteries due to substances in the CSF, imbalance in prostacyclin/thromboxane A_2, penetration of vasoactive substances from blood into the smooth muscle through damaged endothelium, and denervation hypersensitivity.
2 Vasculopathy, either proliferative, immunoreactive, or inflammatory in origin resulting alterations in the media of the vessels.
3 Mechanical compression or distortion of the arteries by the periarterial clot.

A brief review of the recent literature reveals at least 25 putative vasoconstrictors which have been identified in various experimental models. The interested reader is referred to the review by Kassell *et al.*[1]

Measurement of cerebral blood flow

Delayed cerebral ischaemia is associated with angiographic evidence of severe focal or generalized narrowing of the major extraparenchymal arteries (Figure 4). Radiological evidence of vascular spasm occurs in 70% of patients with aneurysmal SAH, but is accompanied by delayed cerebral ischaemia in only 20–30% of patients.[1] There are several reasons why vascular spasm does not cause ischaemia more frequently.

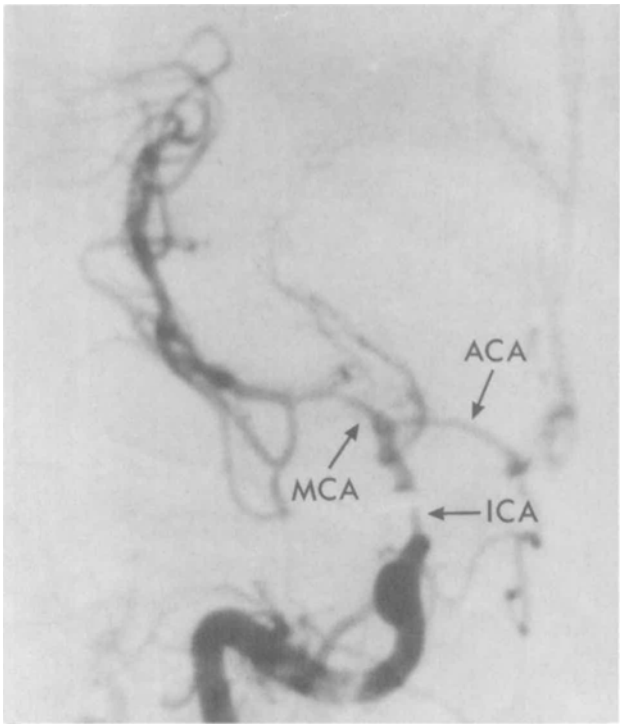

FIGURE 4 Carotid angiogram showing spasm of the supraclinoid portion of the internal carotid artery (ICA), of the anterior cerebral artery (ACA) and of the middle cerebral artery (MCA).

Firstly, the vessels which are prone to spasm are the conducting arteries, where a large reduction in vascular diameter can occur without reducing flow. The term "conducting" indicates that these vessels are not the major site of precapillary resistance, although in the brain, because of their long length, the "conducting vessels" contribute more to the precapillary vascular resistance (60–70%)[26] than in many other vascular beds. Cerebral blood flow is reduced when the angiographic diameter of these arteries is decreased by 50% or more (severe vasospasm) compared with control.[27] This is similar to the findings in the coronary circulation in which a stenosis of greater than 60% of the diameter of the lumen is necessary to reduce coronary flow reserve.[28] Vasospasm which reduces vascular diameter by 25–50% (slight),[27] or less than 25% produces no reduction in CBF beyond that associated with SAH alone.[27]

Secondly, dilatation of intraparenchymal cerebral resistance vessels is thought to occur following spasm of the

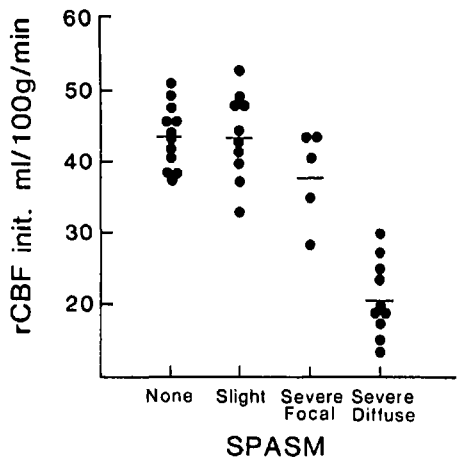

FIGURE 5 Regional cerebral blood flow (rCBF init.), determined using xenon washout with regional counters and the initial slope technique of analysis, in relationship to the symptoms of focal or diffuse cerebral ischaemia. Reproduced with permission from Volby B *et al.*[27]

larger vessels,[8] perhaps compensating in part for the increase in resistance in the larger arteries.

Thirdly, the anatomical location of the vascular spasm and the adequacy of collateral circulation are major factors in determining whether vasospasm which reduces CBF will produce symptoms of cerebral ischaemia.[1]

For these reasons, the angiographic diameters of blood vessels are not sensitive indicators of either cerebral blood flow or symptoms from vasospasm. A recent study[29] using positron emission tomography evaluated the reduction of regional CBF in patients with vasospasm. Patients with focal neurological deficits in association with vasospasm had regional CBF values within the 10 to 20 ml · 100 $g^{-1} \cdot min^{-1}$ range; regional values of CBF of less than 12 ml · 100 $g^{-1} \cdot min^{-1}$ were associated with clinical deficits that were not reversible.[29] Regional CBF, measured by positron emission tomography, in normal brain is 31–84 ml · 100 $g^{-1} \cdot min^{-1}$.[29] Similarly, patients who are stuporous because of severe diffuse vasospasm (Grade IV, Hunt and Hess classification) have profoundly reduced CBF (10–30 ml · 100 $g^{-1} \cdot min^{-1}$) (Figure 5).[29]

Recently, the introduction of the transcranial Doppler (TCD) sonography technique[30] has permitted the measurement of blood flow velocity in the large extracerebral arteries of the brain.

With spasm of the extracerebral vessels following subarachnoid haemorrhage, blood flow velocity usually increases in response to narrowing of the vessels, and this inverse relationship between blood flow velocity and blood vessel diameter has been demonstrated for the middle cerebral and internal carotid arteries.[31] Under these circumstances, cerebral blood flow varies inversely with the blood flow velocity in the spastic vessel.

The non-invasive nature of the device permits repeated measurements at frequent intervals, and the technique may be an effective screening test to identify asymptomatic patients with vasospasm.

TIME COURSE OF VASOSPASM

Vascular narrowing is rarely seen on angiograms before the fourth day after the ictus and is worst at about the seventh day.[32] The percentage probability of symptoms (Figure 2) shows a similar pattern.

Studies using TCD sonography reveal that flow velocity starts to increase by the second post-ictal day, reaches a plateau between the sixth and ninth day, and remains elevated for 15–30 days, depending upon the amount of blood in the basal cisterns on CT scan.[27,33] In contrast to the results from experimental subarachnoid haemorrhage, SAH in humans does not appear to have a biphasic (immediate and delayed) vasospastic response to haemorrhage, since blood flow velocities are not increased in the first 12 hours after the ictus.[34]

Induced hypotension and hyperventilation

AUTOREGULATION

Neurosurgeons may request systemic hypotension to facilitate the dissection and clipping of a cerebral aneurysm. We are unaware of any prospective controlled studies of the effect of induced hypotension during cerebral aneurysm surgery on clinical outcome. To guide his application of induced hypotension, the clinician may then turn to physiological studies which have attempted to evaluate the effect of hypotension on cerebral blood flow and cerebral metabolism.

Autoregulation protects the normal brain against ischaemia caused by decreased blood pressure. This is the phenomenon by which the cerebral resistance vessels dilate in response to decreases in arterial blood pressure or increases in intracranial pressure[4,8,35] and thereby maintain CBF throughout the range of blood pressure experienced under normal physiological conditions.

Autoregulation is disrupted following subarachnoid haemorrhage in patients with vasospasm, and cerebral blood flow may fall in response to only minor decreases in blood pressure. In the first week following subarachnoid haemorrhage, a 10–20% reduction of mean arterial pressure using trimetaphan or sodium nitroprusside decreased cerebral blood flow in patients with angiographically documented vasospasm.[36] Patients without vasospasm demonstrated intact autoregulation.

If the reduction in resting CBF is only mild, increased oxygen extraction by the brain may compensate for

decreased blood flow.[37] Voldby and colleagues,[37] in a study of patients following subarachnoid haemorrhage, measured the effects of hypotension on cerebral metabolic rate for oxygen, and found that the decreases in CBF were offset by increases in arteriovenous oxygen difference and no changes in cerebral oxygen consumption were observed. It is important to note that in their study only patients with resting CBF values in excess of 25 ml · 100 $g^{-1} \cdot min^{-1}$ were subjected to hypotension. Autoregulation was considerably diminished in Grade I and II patients during the first week following subarachnoid haemorrhage whereas autoregulation was intact in Grade I and II patients operated from nine days to three months post-subarachnoid haemorrhage. In this study[37] no information was given concerning the presence or absence of vasospasm.

The results of these studies support the hypothesis that some patients with asymptomatic vasospasm have reduced flow which is nonetheless sufficient to maintain function, while the cerebral blood flow in those who become symptomatic is below the ischaemic threshold.[8] The compensatory mechanisms which permit normal cerebral function with decreased CBF include increased oxygen extraction, and collateral flow, likely encouraged by dilation in the intraparenchymal resistance vessels in response to decreased flow.[8] Since these vessels, which are responsible for autoregulation, are already maximally dilated, a decrease in CBF is observed during induced hypotension. Similarly, since these vessels are dilated because of local factors generated by the low blood flow, little vasoconstriction occurs when blood pressure is raised, and consequently CBF increases passively. Because, as outlined above, the decrease in CBF correlates with increasing clinical grade, Grade III and IV patients are those at greatest risk from hypotension, but even the cerebral vasculature in good grade patients responds poorly to changes in blood pressure during the first week after subarachnoid haemorrhage.[36]

Induced arterial hypotension is requested during manipulation of the aneurysm in the hope of reducing the risk of rupture of the aneurysm during dissection, an event which has been reported to occur in 19% of cases.[18] During controlled hypotension, mean arterial pressures of 50–60 mmHg are commonly well tolerated by patients with normal cerebral vasculature. Global cerebral blood flow is well maintained at these pressures when a variety of hypotensive agents is used.[39,40] Isoflurane has been shown to maintain CBF during hypotension (mean arterial pressure: 50–55 mmHg) while reducing global $CMRO_2$ by approximately 25%.[41] The presence of vasospasm, however, has important implications for the anaesthetist since blood pressure, together with $PaCO_2$[42] and retraction pressure[43] are major factors influencing cerebral blood flow during induced hypotension in these patients. Intraoperative measurement of cerebral blood flow on the operated side poses many technical problems, and the only study of which we are aware measured blood flow contralateral to the surgery.[44] Deliberate hypotension to a mean arterial pressure of 30–40 mmHg in patients with angiographic evidence of vasospasm has been shown to cause severe reduction in CBF, to as low as 20 ml · 100 $g^{-1} \cdot min^{-1}$. Accordingly some neurosurgeons and neuroanaesthetists restrict deliberate hypotension to periods as brief as possible during aneurysm clipping. In patients with vasospasm, deliberate hypotension is avoided if feasible; and the use of temporary clipping of the parent vessel may in some cases allow surgical control without systemic hypotension.[45] A retrospective study[46] has suggested that poor immediate outcomes in operated patients were associated with systolic blood pressures below 60 mmHg for longer than 15 min, although in this study there was no control for surgical factors.

These findings have led some neurosurgeons to abandon prolonged and profound induced hypotension during the approach to cerebral aneurysms. In the absence of controlled trials to assess the value of induced hypotension in cerebral aneurysm surgery, some experts have cautioned that induced hypotension should be applied for the briefest time and degree compatible with safe surgical practice.[47]

HYPERVENTILATION AND CO_2 REACTIVITY

Difficulties similar to those with induced hypotension confront the clinician who is assessing the potential consequences of decreasing the $PaCO_2$ with hyperventilation in the patient with a subarachnoid haemorrhage. The surgical approach to the aneurysm usually requires retraction of brain tissue in order to expose the vessels at the base of the brain. This exposure may be facilitated through positioning of the patient, withdrawal of CSF, and dehydration with mannitol. More controversial is the use of hyperventilation.

Induced hypocapnia is commonly used in neurosurgical procedures to reduce cerebral blood flow and volume and intracranial pressure. The use of induced hypocapnia in patients with subarachnoid haemorrhage (at risk for cerebral ischaemia) has not been assessed by a prospective controlled trial. Consequently the clinician must attempt to extrapolate the effect of hypocapnia on CBF in these patients from physiological studies. These studies fall under the general heading of CO_2 reactivity.

Vasoconstriction in response to hypocapnia and vasodilatation in response to hypercapnia constitute the normal response of the cerebral vasculature to changes in $PaCO_2$. Cerebral blood volume and flow both decrease when the $PaCO_2$ is lowered,[48] hence induced hypocapnia

may be used to reduce intracranial pressure. The effect of hypocapnia on spastic cerebral vessels is controversial, but Voldby *et al.*[37] observed that vasoconstriction was enhanced by hypocapnia in patients with severe diffuse vasospasm. Although this would appear to confirm the detrimental effect of hypocapnia in these patients, it has been shown that in the sickest individuals (Grades III and IV, with intracranial hypertension and CSF lactic acidosis), hyperventilation increased cerebral perfusion pressure and cerebral oxygen consumption.[37]

These contradictory results suggest that the effects of hyperventilation on cerebral perfusion are the sum of the increase in perfusion pressure associated with the reduction in intracranial pressure balanced against the increase in vascular resistance caused by the hypocapnia.

Therefore, the selection of patients who might benefit from hyperventilation is difficult, particularly since CBF may vary considerably in different brain regions in patients with vasospasm. The role of hyperventilation in patients with SAH remains unresolved, although it has been recommended that normocapnia ($PaCO_2$ 35–45 mmHg) be maintained during induced hypotension.[49]

Therapy for cerebral vasospasm

Current therapy for prevention and treatment of cerebral ischaemia from vasospasm can be grouped into treatment to dilate the spastic vessels, to improve the flow characteristics of the blood (haemodilution), and to increase flow by increasing the perfusion pressure, either by increasing the systemic arterial pressure or by increasing the pulse pressure.[50] Specific therapy for the prevention or reversal of the vascular narrowing awaits the clarification of the pathogenesis of vasospasm. Despite extensive research for the past two decades,[51] direct pharmacological dilatation of the spastic vessels, with the possible exception of calcium antagonists, has not been found useful.[1]

Calcium antagonists

The current hypotheses concerning the development of tension in vascular smooth muscle suggest that a key initiating event is the elevation of intracellular Ca^{++} in response to chemical, mechanical or electrical stimulation. This may occur by influx of calcium from the extracellular fluid or by mobilization of intracellular stores. Three major pathways for passage of Ca^{++} into the cell are by leakage, through receptor-mediated channels, and through voltage-mediated channels. The voltage-mediated channels are thought to be responsible for the initial rise in intracellular calcium during the propagation of a normal action potential in smooth muscle. One of the subtypes of voltage-sensitive channels, termed the large or L-type Ca^{++} channel, is sensitive to blockade by drugs of the 1,4-dihydropyridine class such as nimodipine and nicardipine. The L channels are found in abundance and probably have functional importance in vascular smooth muscle and excitable cells in the heart, brain and skeletal muscle.[52] The activity of dihydropyridines at L channels combined with the high lipid solubility of nimodipine and nicardipine which allows these drugs to penetrate the blood brain barrier has selected them for use in the treatment of cerebral vasospasm. The exact mechanism by which the dihydropyridines act in cerebral ischaemia is not established. The cerebrovascular and cerebral effects of nimodipine have been recently reviewed.[53,54]

PREVENTION OF DELAYED CEREBRAL ISCHAEMIA

Several prospective, blinded, placebo-controlled trials have evaluated the effectiveness of nimodipine in preventing delayed cerebral ischaemia or in reducing morbidity and mortality from vasospasm. These trials have been reviewed in detail[55] and only the most prominent will be outlined here. In general, the studies support the conclusion that nimodipine, when given soon after subarachnoid haemorrhage, reduces the number of poor outcomes due to vasospasm.

The first report, by Allen and coworkers, showed that oral nimodipine (0.7 $mg \cdot kg^{-1}$ loading dose followed by 0.35 $mg \cdot kg^{-1}$ every four hours) reduced the occurrence of severe neurological deficits and mortality from vasospasm.[56] A prospective trial in poor grade aneurysm patients (Grades III–V)[57] confirmed that patients receiving oral nimodipine therapy (90 mg every four hours) had a better outcome at three months after subarachnoid haemorrhage and fewer delayed ischaemic deficits from vasospasm. In this study, the improvements occurred in patients in Hunt and Hess Grades III and IV. In a large trial, Pickard *et al.* found that oral nimodipine (60 mg four-hourly) reduced the frequency of cerebral infarction from 33% (placebo) to 22% and reduced the percentage of poor outcomes from 33% (placebo) to 20%.[58] Although nimodipine did not change the angiographic diameter in the spastic vessels,[56,57] intravenous nimodipine (2 $mg \cdot hr^{-1}$) did reduce the severity of the vasoconstriction as assessed by transcranial Doppler sonography.[30]

TREATMENT OF SYMPTOMATIC DELAYED CEREBRAL ISCHAEMIA

Limited experience with the use of nimodipine to relieve established symptomatic ischaemia from vasospasm is encouraging. Jan *et al.* reported a randomized, double-blinded, placebo-controlled study of nimodipine (0.03 $mg \cdot kg^{-1} \cdot hr^{-1}$) administered *iv* within 24 hr of the onset of symptoms of delayed cerebral ischaemia.[59] Nimodipine therapy was associated with a reduction in mortality and severe morbidity from vasospasm, but the efficacy

did not appear to be as striking as in the studies concerning the prophylactic use of nimodipine outlined above.

IMPLICATIONS FOR ANAESTHETIC MANAGEMENT

Prophylactic therapy with calcium antagonists does not appear to require any major alterations of anaesthetic management during surgery for aneurysm clipping. For patients receiving oral prophylactic nimodipine therapy[60] (0.7 $mg \cdot kg^{-1}$ loading dose + 0.35 mg^{-1} four-hourly) anaesthetic requirements, blood loss, and the dose of nitroprusside to maintain hypotension were not different from the patients receiving placebo. Minimum systolic blood pressure recorded during the period of decreased stimulation after tracheal intubation was less in the nimodipine group. Warner *et al.*[61] reported that *iv* nicardipine for vasospasm prophylaxis did not make intraoperative haemodynamic management more difficult, but decreased the necessity for isoflurane to control blood pressure during balanced anaesthesia.

Haemodilution

Haemodilution has been proposed as a component of therapy for improving cerebral blood flow to brain regions affected by vasospasm. Since there have been no randomized controlled trials evaluating the effectiveness of haemodilution in vasospasm published, we will summarize the theoretical basis for these treatments and the limited information that is currently available from uncontrolled trials.

The haematocrit (Hct) is the most important determinant of whole blood viscosity.[62] Although the majority of human and animal studies show that CBF increases following haemodilution, there is considerable debate as to whether it is the oxygen delivery (active vasodilatation of the cerebral vascular bed in response to bulk oxygen transport or tissue PO_2)[63] or the blood viscosity which is the primary determinant of CBF under these conditions.[64] This is of considerable importance because if oxygen delivery is the primary determinant then little therapeutic benefit from haemodilution can be expected. Recent work supports the hypothesis that blood viscosity and CaO_2 are independent variables. In a study in lambs in which CaO_2 and Hct were varied separately, Hudak *et al.*[47] showed that increasing the Hct from 20 to 40% decreased CBF independently of changes in oxygen content. The authors cautioned that the mechanism(s) of the effect of Hct on cerebral blood flow may or may not be related to viscosity. The implication of these findings is that if CaO_2 and Hct are independent determinants of CBF, then the increase in flow which is observed when the Hct is decreased is only partly (56% in Hudak *et al.*[47]) due to the decrease in RBC concentration (possibly a viscosity effect), the remaining increase being related to the decrease in CaO_2.

The optimum haematocrit for oxygen delivery to the brain remains controversial, with 30–32% favoured by some authors[48,49] while 40–45% is the range suggested by others.[65] Some investigators have reported that the total body oxygen transport was maximal at Hct values of 30–33%[65,66] and this finding has been used to explain increases in cerebral blood flow observed during haemodilution and to suggest that 30% is the optimal Hct for cerebral oxygen delivery. In a review of the published human experimental data concerning oxygen delivery and haematocrit, Gaehtgens and Marx[67] have concluded that the optimal haematocrit for oxygen delivery to the brain is approximately 42% and that haemodilution below the physiological level would tend to reduce tissue oxygen supply. Inspection of the summarized data[67] (Figure 6) reveals that there is a range of Hct (35%–50%) over which cerebral O_2 delivery is normal. At Hct values greater than this, the increase in CaO_2 is more than offset by the increased viscosity while at Hct values below this range, the decreased O_2 carrying capacity is not offset by decreased viscosity. In an experimental study designed to evaluate directly the effect of haemodilution on tissue oxygenation Chan *et al.*[68] demonstrated that a progressive decrease in haematocrit from 40 to 20% did not increase tissue PO_2 in normal brain or in brain made ischaemic by middle cerebral artery occlusion.

Haemodilution in isolation has not been studied in patients with vasospasm, but has been the subject of several therapeutic trials in thrombo-occlusive stroke, which have been summarized by Gottstein.[69] Haemodilution was associated with increases in cerebral blood flow in both normal and infarcted brain regions. The elevated Hct values in thrombo-occlusive stroke (range of mean values in six trials 44–48%) reflect the fact that the risk of cerebral infarction is proportional to the Hct,[70] and thus the reduction of haematocrit by haemodilution in patients with high Hct and acute ischaemic stroke appears to be reasonable.[67]

Despite this sound theoretical basis, outcome studies of haemodilution therapy in acute ischaemic stroke have shown mixed results.[71–74] Thus, in terms of clinical outcome, there is no firm support for haemodilution therapy in acute ischaemic stroke, the only form of cerebral ischaemia in which it has been evaluated in isolation from induced arterial hypertension. In contrast to patients with acute ischaemic stroke (Hct 44–48%),[69] patients with aneurysmal subarachnoid haemorrhage do not have an increased Hct. Mean Hct values reported in three clinical studies were 37%, 38%, and 39%.[75–77] Therefore, since Hct levels are not usually elevated,

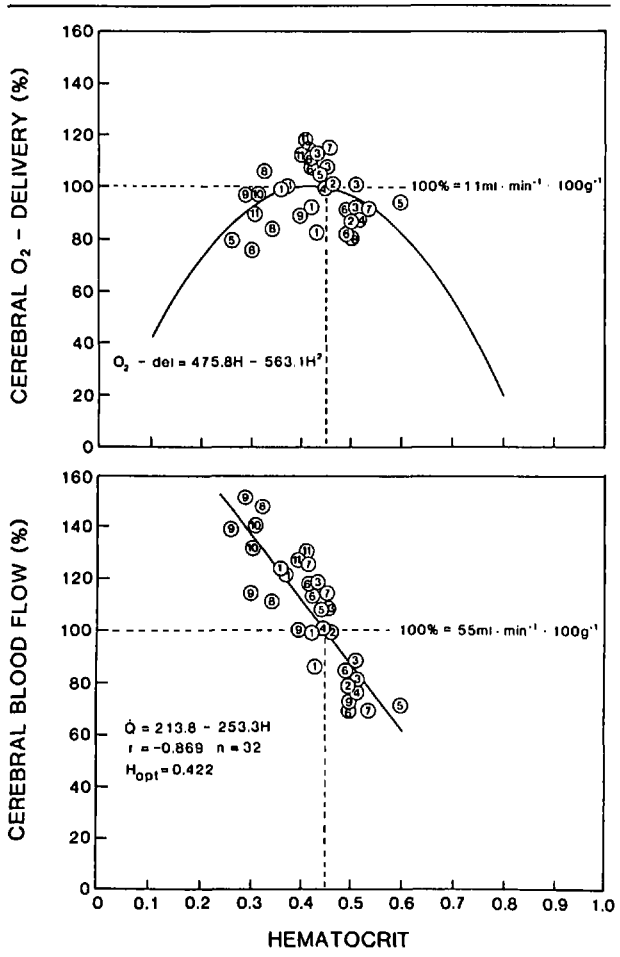

FIGURE 6 (Top): Effect of haematocrit on cerebral O_2 delivery, calculated on the basis of the data in the bottom. The calculation assures constant arterial O_2 saturation and proportionality between haematocrit and haemoglobin concentration in the blood. The relationship indicates an optimal haematocrit (H_{opt}) at 0.422. (Bottom): Changes of cerebral blood flow as a function of systemic haematocrit. Data from measurements in human patients by various authors (numbers are for references in original review[67]) in . Blood flow data are expressed relative to a control value (100% = 55 ml · min^{-1} · 100 g^{-1}) at a haematocrit of 0.45. Figure copied from P. Gaehtgens and P. Marx,[67] with permission.

patients with subarachnoid haemorrhage, at least as a group, are less suitable candidates for haemodilution therapy than are stroke patients. Since the published data[67] suggest that oxygen delivery is well maintained between haematocrit values of 35–45%, this range would seem to be a prudent goal for transfusion therapy in patients at risk for cerebral ischaemia.

Systemic arterial hypertension

Induced systemic arterial hypertension has been proposed as a treatment for cerebrovascular insufficiency for over 20 yr. Under normal conditions, changes in arterial pressure are modulated by the autoregulatory response in the cerebral vessels so that, within the normal physiological range, cerebral blood flow is maintained at the level set by the metabolic needs of the tissue and is independent of arterial pressure. Under ischaemic conditions, the vessels are maximally dilated, and consequently flow in these arteries becomes proportional to the perfusion pressure.

Increasing arterial pressure could reverse cerebral ischaemia by mechanically increasing perfusion pressure and hence blood flow across the stenotic segment,[78] or by improving collateral flow to the ischaemic region.[79] It is important to recall that a neurological deficit may represent cerebral ischaemia and not infarction. Under conditions of focal partial ischaemia, the effects of reduced CBF are both flow- and time-dependent. In an experimental study,[80] ischaemic cerebral oedema occurred if cerebral blood flow was reduced to less than 40% of the normal value for more than 30 min. Reperfusion of the ischaemic region before this has been thought to lead to improvement of neurological function in both the experimental and the clinical setting.[81,82]

The use of *iv* vasopressors to increase systemic pressure without constricting the cerebral arteries is based on the concept of metabolic regulation of the blood supply of the brain,[83] which has traditionally held that, blood flow to the brain is regulated by local metabolic needs and is not affected by changes in autonomic tone. Although the role of neurotransmitters in the control of the cerebral circulation is not well understood, the insensitivity of CBF to changes in autonomic tone is not due to a lack of neurotransmitter receptors or innervation in the cerebral vasculature.[84] In fact, the conducting arteries, resistance arterioles and even the capillaries have a rich innervation with peptidergic neurons, and at least ten putative neurotransmitters have been identified.[85] Failure of circulating monoamines (noradrenaline, adrenaline, dopamine, serotonin) to have a direct effect on the cerebral vasculature may be related to the cerebral endothelial cells, which form both a morphological barrier at the luminal membrane and neurochemical blood-brain barrier through cytoplasmic O-methylation and deamination of the small quantities of monoamines which penetrate the endothelial cell, thereby preventing the monoamines from interacting with the cerebrovascular smooth muscle.[86]

Unfortunately there have been no controlled trials of induced arterial hypertension in patients with delayed cerebral ischaemia. As with stroke, outcome studies of patients with vasospasm require control groups, since the evolution of the ischaemia is highly variable. Historical control groups are not suitable since the supportive care

available to patients has changed greatly over the past decade. At present, the most persuasive evidence supporting the use of induced arterial hypertension for the treatment of delayed cerebral ischaemia from cerebral vasospasm comes from case reports in which each patient serves as his/her own control. This has been demonstrated by Muizelaar and Becker[77] who provided detailed reports of five patients with symptomatic vasospasm treated with hypertension induced with phenylephrine. Four patients showed an immediate clinical improvement following the onset of treatment. The average CBF in the affected hemisphere for these four patients was 18.8 $ml \cdot 100\,g^{-1} \cdot min^{-1}$ before treatment and 30.8 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ after induced hypertension. Blood pressure was raised until symptoms improved and was maintained at that level until reduction of blood pressure did not cause neurological deterioration. In the four patients this represented an increase in average mean arterial pressure from a value of 102 mmHg before treatment to a value of 134 mmHg during therapy. Similar clinical improvement was seen in 43 of 58 patients studied retrospectively.[75]

Therapy in these reports was a combination of intravascular volume expansion and induced arterial hypertension, and the relative importance of each in the reversal of symptoms was not determined. Awad *et al.*[76] also reported the results of hypervolaemic haemodilution and arterial hypertension in 42 patients with symptomatic vasospasm. In that study, systolic blood pressure was altered according to predetermined ranges, 160–200 mmHg with the cerebral aneurysm clipped, 120–150 mmHg with the aneurysm unclipped. In 26 cases these goals were attained spontaneously by the patient or upon withdrawal of antihypertensive medication and only 16 patients required vasopressor therapy to achieve the desired blood pressure.

Thus in these three reports of successful haemodynamic management of cerebral ischaemia from vasospasm, induced arterial hypertension was a major component of therapy.

The intraoperative use of induced hypertension to preserve neurological function in patients with symptomatic vasospasm is in its infancy and the only reports of which we are aware are anecdotal.[87,88]

Blood volume expansion

Before the current interest in early surgery for SAH patients, bed rest with fluid restriction and antifibrinolytic therapy were the mainstays of therapy. Although antifibrinolytic therapy with tranexamic acid did reduce the rate of rebleeding during the first three months from 24% to 9% this improvement was offset by an increase in ischaemic complications from 15% to 24%.[89] As outlined above, these conditions lead to decreased total blood volume (TBV), which, in prospective trials, has been shown to be associated with an increased risk of cerebral ischaemia from vasospasm.[90,91]

These findings have lead to the recommendation that blood volume be monitored and maintained in patients following subarachnoid haemorrhage.[12] Blood volumes maybe measured by the indicator dilution technique, commonly using ^{51}Cr or ^{99}Tc and radioiodinated human serum albumin as indicators for the red cell and plasma volumes respectively. Total blood volume may be estimated from measurement of either red cell volume or plasma volume using the peripheral venous haematocrit, having corrected for the difference between the venous and total body haematocrit. Unfortunately, estimates of blood and plasma volume based on body weight are notoriously inaccurate due to interpersonal variations in body composition. It is therefore difficult to establish a range of normal values sufficiently narrow to be useful in clinical practice. The most accurate method at present would appear to be to measure both plasma and red cell volumes serially and so to use each patient as his own control. While this may be a useful research method, it has not had widespread clinical application since being supplanted by measurements of cardiac filling pressures over 25 yr ago.[92] Estimates of blood volume based on measurements of total body water as an index of lean body mass appear to be a promising alternative, which is sufficiently simple for clinical practice.[12]

Blood volume measurements have not been commonly used to guide therapy of vasospasm in clinical practice. Since many clinicians feel that the mechanism by which neurological improvement is achieved with volume expansion is through an increase in cardiac output,[93] they have used right- or left-sided cardiac filling pressures (central venous pressure, CVP, or pulmonary artery wedge pressure, P_{PAW}) as the end-points for volume expansion. Usually the assumption is made that the cardiac filling pressures correlate with the total blood volume of the patient, and that the cardiac output will increase in response to increments in the cardiac filling pressures by the Frank-Starling mechanism. Commonly chosen end-points for therapy include a positive fluid balance with a CVP of approximately 10 mmHg and/or a P_{PAW} of 18–20 mmHg.

Many neurosurgeons have felt that delayed cerebral ischaemia can be provoked by decreases in blood volume even when blood pressure does not change,[94–96] and have noted improvement in neurological function when blood volume was returned to normal or supernormal levels. Kindt *et al.*, while using induced arterial hypertension in the treatment of patients with delayed cerebral ischaemia, noted that most of the patients had low central venous pressures and clinical evidence of dehydration.[96] In

uncontrolled trials, intravascular volume expansion, independent of arterial hypertension, has been reported to be effective in the treatment of cerebral ischaemia secondary to cerebral vasospasm.[89,96] Since these early reports, blood volume expansion, often in conjunction with arterial hypertension and haemodilution, has become a popular treatment for delayed cerebral ischaemia associated with cerebral vasospasm[75,76] and prophylactic volume expansion has been proposed to reduce delayed cerebral ischaemia following early aneurysm surgery.[97] Although the majority of clinical reports support the efficacy of volume expansion, the studies are poorly controlled, and many different protocols have been used for volume expansion. Consequently the usefulness of volume expansion remains controversial.[98]

Complications of therapy

Complications of therapy may be neurological or systemic. Although there is a theoretical risk of increasing cerebral oedema and intracranial pressure when hypertension is induced in a patient with cerebral ischaemia or infarction this does not appear to be a clinical problem.[75,76,79] Rebleeding has occurred during hypertensive therapy, but it is not known whether the therapy contributed to the rebleeding.

The induction of hypervolaemic hypertension is a physiological stress and the body defends itself vigorously. In one of the most widely quoted studies,[75] attempts were made to maintain a 20–100 mmHg increase in systolic blood pressure, along with a PCWP of 18–20 mmHg. Reflex bradycardia and pronounced diuresis were common, prompting treatment with atropine, vasopressin and fludrocortisone in order to maintain hypervolaemia and hypertension.

In this setting, one must be alert for the development of cardiovascular complications, principally pulmonary oedema and myocardial ischaemia and infarction, as well as complications arising from invasive monitoring devices. In one study,[75] cardiovascular complications occurred in 11/58 patients – ten patients developed pulmonary oedema, two of these were symptomatic while eight were diagnosed by chest *x*-ray. Two patients developed coagulopathies which were attributed to low molecular weight dextran administration. One of these patients died from a haemothorax related to a subclavian puncture for Swan Ganz catheter insertion. Dilutional hyponatraemia (serum sodium $< 120\ mEq \cdot L^{-1}$) was attributed to water intoxication in two patients. In another study,[76] 3/39 patients developed pulmonary oedema. One patient required tracheal intubation and all had an excellent recovery. In the latter study there were no complications of invasive monitoring.

Are patients with subarachnoid haemorrhage at increased risk for cardiac complications? Acute cardiac disease has not been identified as a factor influencing outcome,[99,100] but pathological findings in patients who have died following SAH have revealed an increased frequency of subendocardial damage.[100] The massive sympathetic response to a severe subarachnoid haemorrhage (Figure 2) may lead to myocardial ischaemia or infarction, evidence of which ranges from subendocardial haemorrhages to transmural myocardial infarction,[100] but the significance of such lesions in these patients is unknown.

Diagnosis of myocardial ischaemia after subarachnoid haemorrhage is difficult because patients may be unable to report chest pain. The diagnostic value of the ECG for detecting myocardial ischaemia in patients with SAH not known to have coronary artery disease is unresolved because the prevalence of myocardial ischaemia in this population is not known. The ECG, while frequently abnormal, often shows non-specific changes of the T wave and the ST segment, which some authors[101] feel reflects autonomic imbalance associated with intracranial pathology. Even the presence of pathological Q waves which along with elevated ST segments have been found to indicate a poor prognosis,[102] does not confirm the presence of a myocardial infarction.[103]

During surgery for aneurysm clipping ECG changes are common and occur in 35% of patients.[104,105] Changes in the ST segment and T wave are most frequent, without evidence of cardiac dysfunction or morbidity.[106] However, the response of these patients to the added stress of hypervolaemic haemodilution has not been reported.

Guidelines for volume expansion.

From the above discussion it is apparent that there is an urgent need for randomized, prospective, controlled trials of volume expansion in the prevention and treatment of cerebral ischaemia due to vasospasm. In the absence of such trials, the clinician must proceed with a plan based upon the limited information which is available. As anaesthetists, we are often responsible for patients in whom therapy with hypertension and/or hypervolaemia has already been initiated.

For a patient with a new neurological deficit, during manipulation of the variables which influence cerebral oxygen delivery, the most reasonable end-point to choose is that of neurological function. If permanent damage is to be avoided, therapy must be instituted as rapidly as possible, since the risk of permanent neurological damage is both flow- and time-related. The goals of therapy are-based upon the patient's current blood pressure, Hct, blood gas analysis and right and left-sided cardiac filling pressures. If volume loading is chosen, chosen volume should be infused over a short time such as 20 min[107] to

TABLE IIa Guidelines[107] for fluid challenge utilizing central venous pressure monitoring

Observation	*CVP, cmH_2O*	*Fluid challenge*
Observe CVP for 10 minutes	<8 cm H_2O	200 ml over 10 min
	<14 cm H_2O	100 ml over 10 min
	≥14 cm H_2O	50 ml × 10 min
Increase during infusion 0–9 min	>5 cm	Stop
Increase after infusion	>2 cm <5 cm	Wait 10 min
	≤2 cm	Continue infusion

TABLE IIb Guidelines for fluid challenge utilizing pulmonary artery diastolic or pulmonary artery wedge pressure monitoring

Observation	*P_{PAW}, P_{PAD}*	*Fluid challenge*
Observe for 10 min	<12 mmHg	200 ml × 10 min
	<16 mmHg	100 ml × 10 min
	≥16 mmHg	50 ml × 10 min
Increase during infusion 0–9 min	>7 mmHg	Stop
Increase following infusion	>3<7 mmHg	Wait 10 min
	≤3 mmHg	Continue infusion

determine whether change in cardiac function has occurred. Guidelines have been provided for volume loading with crystalloid in patients in shock using both central venous pressure and pulmonary wedge pressure (PWP) values (Table II),[107] and might be applied acutely to patients with symptomatic vasospasm.

Is it likely that changes in colloid osmotic pressure associated with volume expansion will aggravate ischaemic cerebral oedema in these patients and if so, are there any differences in this regard between crystalloids and colloids?

The characteristics of oedema following cerebral ischaemia have been recently reviewed by Pappius.[108] In the cytotoxic phase, in which the fluid accumulation is intracellular with no expansion of the extracellular space, it is unlikely that COP is an important factor in oedema formation.[109] Rather, it is during the vasogenic phase of oedema, which occurs if cerebral ischaemia is sufficiently prolonged and severe,[108] that plasma with a higher COP than the brain extracellular fluid might extract fluid from oedematous brain tissue.[109] This effect depends upon the porosity of the cerebral capillaries being sufficiently small so as to allow the COP gradient to be established across the capillaries.[109]

We are unaware of any studies of this issue in patients with subarachnoid haemorrhage or vasospasm. In patients with acute strokes, Matthews *et al.*[72] noted a decrease in early mortality in patients treated with colloid, and attributed the improvement to the prevention or reversal of cerebral oedema. Animal studies of the consequences of haemodilution on cerebral oedema caused by ischaemia,[110] or cold[111–113] have yielded mixed results, with two studies[110,111] suggesting more oedema formed with crystalloid volume expansion and two[112,113] showing no difference between colloids and crystalloids. The difference in osmolarity between commercial preparations of crystalloid solutions and colloids has been proposed as the cause of the greater oedema seen with crystalloid haemodilution.[114,115]

Conclusions

Recent developments in intensive care are presently being applied to patients at risk of delayed cerebral ischaemia following subarachnoid haemorrhage. Early surgery to secure the aneurysm gives the clinician freedom to apply therapy designed to increase cerebral perfusion pressure, blood volume and cardiac output. Nimodipine is effective in preventing or treating delayed cerebral ischaemia and appears to require few alterations in anaesthetic management. Prospective trials are urgently required to evaluate the effectiveness of the independent contributions of haemodynamic and rheologically-based therapy for delayed cerebral ischaemia from vasospasm.

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