Review Article

Vasodilators during cerebral aneurysm surgery

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The objective of this review is to review the anaesthetic implications of vasoactive compounds particularly with regard to the cerebral circulation and their clinical importance for the practicing anaesthetist. Material was selected on the basis of validity and application to clinical practice and animal studies were selected only if human studies were lacking. Hypotensive drugs have been used to induce hypotension and in the treatment of intraoperative hypertension during cerebral aneurysm surgery. After subarachnoid haemorrhage, cerebral blood flow is reduced and cerebral vasoreactivity is disturbed which may lead to brain ischaemia. Also, cerebral arterial vasospasm decreases cerebral blood flow, and may lead to delayed ischaemic brain damage which is a major problem after subarachnoid haemorrhage. Recently, the use of induced hypotension has decreased although it is still useful in patients with intraoperative aneurysm rupture, giant cerebral aneurysm, fragile aneurysms and multiple cerebral aneurysms. In this review, a variety of vasodilating agents, prostaglandin E_1, sodium nitroprusside, nitroglycerin, trimetaphan, adenosine, calcium antagonists, and inhalational anaesthetics, are discussed for their clinical usefulness. Sodium nitroprusside, nitroglycerin and isoflurane are the drugs of choice for induced hypotension. Prostaglandin E_1, nicardipine and nitroglycerin have the advantage that they do not alter carbon dioxide reactivity. Local cerebral blood flow is increased with nitroglycerin, decreased with trimetaphan and unchanged with prostaglandin E_1. Intraoperative hypertension is a dangerous complication occurring during cerebral aneurysm surgery, but its treatment in association with subarachnoid haemorrhage is complicated in cases of cerebral arterial vasospasm because fluctuations in cerebral blood flow may be exacerbated. Hypertension should be treated immediately to reduce the risk of rebleeding and intraoperative aneurysmal rupture and the choice of drugs is discussed. Although the use of induced hypotension has declined, the control of arterial blood pressure with vasoactive drugs to reduce the risk of intraoperative cerebral aneurysm rupture is a useful technique. Intraoperative hypertension should be treated immediately but the cerebral vascular effects of each vasodilator should be understood before their use as hypotensive agents.

L'objectif de cet article est de revoir les implications anesthésiques des composés vasoactifs particulièrement en rapport avec la circulation cérébrale ainsi que leur importance clinique pour l'anesthésiste. Les agents ont été choisis sur la base de leur validité et de leur application à la pratique clinique et des études animales ont été choisies seulement en l'absence d'étude sur l'homme. Les agents hypotenseurs ont été utilisés pour induire de l'hypotension et pour traiter l'hypertension preopératoire pendant la chirurgie d'anévrisme cérébrale. Après une hémorragie sous-arachnoïdienne, le débit sanguin cérébrale réduit et la vasomotricité cérébrale perturbée peuvent entraîner une ischémie cérébrale. Ainsi, le vasospasme artériel cérébral diminue le débit sanguin cérébral et peut conduire à des dommages cérébraux retardés d'ischémie, problème majeur après une hémorragie sous-arachnoïdienne. Récemment, l'utilisation de l'hypotension contrôlée s'est raréfiée bien qu'elle soit encore utile chez les patients avec une rupture peropératoire d'anévrisme, en cas d'anévrisme cérébral géant, d'anévrismes fragiles et d'anévrismes cérébraux multiples. Dans cet article, une variété de vasodilatateurs, le prostaglandine E_1, le nitroprussiate de sodium, la nitroglycérine, le trimétaphan, l'adénosine, les antagonistes calciques et les agents d'inhalation son discutés pour

Key words

ANAESTHETICS, VOLATILES: isoflurane;
ANAESTHETIC TECHNIQUES: hypotension;
BLOOD PRESSURE: hypotension;
BRAIN: blood flow, carbon dioxide tension;
HORMONES: prostaglandin E_1
SYMPATHETIC NERVOUS SYSTEM: ganglionic blockade, trimetaphan;
PHARMACOLOGY: adenosine, nitroglycerin, nitroprusside, calcium channel blockers, hydralazine, diazoxide, labetalol, esmolol;
COMPLICATIONS: intraoperative hypertension, brain ischaemia, rebleeding.

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leur utilité clinique. Le nitroprussiate de sodium, la nitroglycérine et l'isoflurane sont les agents de choix pour l'hypotension contrôlée. La prostaglandine E_1, la nicardipine et la nitroglycérine ont l'avantage de ne pas altérer la réactivité au dioxyde de carbone. Le débit sanguin cérébral local est augmenté avec la nitroglycérine, diminué avec le trimétaphan et inchangé avec la prostaglandine E_1. L'hypertension peropératoire est une complication dangereuse aux cours d'une chirurgie d'anévrisme cérébral, mais son traitement lors d'hémorragie sous-arachnoïdienne se complique dans les cas de vasospasme artériel cérébral parce que les fluctuations du débit sanguin cérébral peuvent s'exacerber. L'hypertension devrait être traitée immédiatement pour réduire le risque de resaignement et de rupture peropératoire de l'anévrisme. Le choix des agents est discuté. Bien que l'utilisation de l'hypotension contrôlée est moins fréquente, le contrôle de la pression artérielle avec des agents vasoactifs dans le but de réduire le risque de rupture peropératoire d'anévrisme cérébral est une technique courante. L'hypertension peropératoire devrait être traitée immédiatement mais les effets vasculaires cérébraux de chaque vasodilatateurs devraient être compris avant qu'ils soient utilisés comme agents hypotenseurs.

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During the clipping of cerebral arterial aneurysms, induced hypotension is often used to reduce the aneurysmal wall tension to minimize the risk of premature rupture.[1] A primary concern with the use of hypotension has been that cerebral blood flow (CBF) may decrease to critically low levels, resulting in ischaemic damage to the brain. Patients with subarachnoid haemorrhage (SAH) may develop abnormal cerebrovascular reactivity and impaired autoregulation[2,3] and they may be more susceptible to severe flow reductions during hypotension than normal individuals,[4] resulting in global and or focal ischaemia of the brain.[5] During the first two weeks after SAH, several events may make heavy demands on the capacity of the cerebral vasculature to react adequately. Cerebral arterial vasospasm and rebleeding are major problems and cerebral aneurysm surgery is often performed within the same period. Another problem during general anaesthesia for aneurysm clipping is intraoperative hypertension. Intraoperative hypertension may increase the risk of rebleeding and intraoperative aneurysm rupture before its exposure so that intraoperative blood pressure should be well controlled.

Pathophysiology

Subarachnoid haemorrhage

Ten percent of all strokes result from subarachnoid haemorrhage (SAH) which is caused most often by the sudden rupture of an intracranial saccular aneurysm. Subarachnoid haemorrhage chiefly afflicts patients between 40 and 60 yr of age and women are affected more often than men. Rupture of an intracranial arterial aneurysm produces severe focal and generalized disturbances in brain function (Figure 1). Depending on the surgical risk, patients may present a broad spectrum of clinical conditions, ranging from non-ruptured aneurysm (grade 0) to deep coma (Grade V).[6] Delayed cerebral ischaemia is the major cause of poor outcome or death after SAH. The risk of delayed ischaemia and cerebral infarction after SAH is dependent on many factors, the most important of which are the amount of blood in the basal cisterns, the presence of intracranial haematoma and the patient's clinical condition.[7] Subarachnoid haemorrhage from rupture of an intracranial arterial aneurysm produces severe focal and generalized disturbances in brain function. Rupture of a cerebral aneurysm with subsequent arterial bleeding may cause dramatic changes in intracranial pressure (ICP)[8] (Figure 2). In severe haemorrhage, cerebral perfusion pressure may decrease to low levels with a concomitant decrease in cerebral blood flow. Severely elevated ICP may also lead to brain herniation. Following SAH, dilated ventricles can be seen with computerized tomographic (CT) and scanning at admission can be used to classify the severity of haematoma. Computerized tomographic scanning is valuable in identifying the patient's risk of brain ischaemia after SAH.[9]

Brain damage may be caused by a marked increase in intracranial pressure and mechanical distortion of intracranial structures resulting from the sudden injection of blood into the subarachnoid space.[10] Some patients

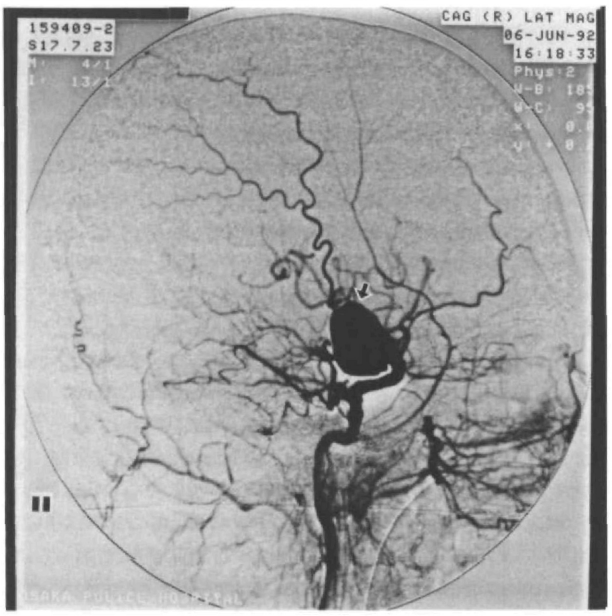

FIGURE 1 Giant cerebral aneurysm (→) originating from internal carotid artery (lateral view) in a 65-yr-old woman.

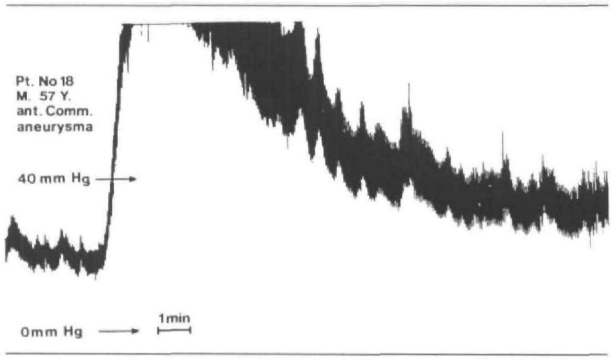

FIGURE 2 Intraventricular pressure during recurrent haemorrhage in 57-yr-old man with anterior communicating artery aneurysm. (from *Voldby B.* Alterations in vasomotor reactivity in subarachnoid hemorrhage. *In:* Wood JH (Ed.). Cerebral blood flow. McGraw-Hill Book Company 1987; 404.)

have symptoms consistent with hydrocephalus.[11] The most predictable factors for the development of hydrocephalus are age, hypertension, CT findings of hydrocephalus, and intraventricular haemorrhage. In order to reduce ICP and to reduce the risk of brain herniation, cerebrospinal drainage can be considered, but this is controversial.[12] Subarachnoid haemorrhage causes a considerable decrease in both CBF and metabolism.[13-15] The reduction in regional CBF and metabolism may occur even in patients in good clinical condition and without vasospasm. Patients in poorer clinical condition have more marked reduction of CBF and metabolism. Mountz *et al.*[16] performed 101 quantitative bedside CBF measurements on 40 patients to correlate the severity of SAH with CBF. In patients with low-grade SAH, global CBF was within normal limits before and after surgery but increased for two weeks postoperatively, while in the patients with high-grade SAH there was no increase in CBF one week after surgery. Voldby *et al.* reported that the cerebral metabolic rate of oxygen ($CMRO_2$) was more severely reduced than regional CBF during the first two weeks after SAH.[17] The most marked depressions of $CMRO_2$ and regional CBF were seen with the development of focal neurological deficits.[14,17]

The complications associated with SAH are complex and include cerebral oedema, increased ICP, diffuse cerebral ischaemia, rebleeding, cerebral arterial vasospasm and hydrocephalus. The presence of oedema, hydrocephalus, and intracranial hypertension following SAH may cause regional CBF and cerebral metabolism to deteriorate even further.[18,19] Neurological status after SAH is evaluated by the classification of Hunt and Hess[20] (Table I). The Glasgow Outcome Scale[21] is often used to determine the outcome of patients with head trauma. In general, the probability of survival for each of the grades of the Hunt and Hess system increases with the interval between the initial haemorrhage and the time that the clinical grade is determined.[22] For example a patient graded I on the first day after the SAH has a 65% chance of survival, whereas a similar grading 21 days later indicates a 95% chance of surviving.[23] The operative results from delayed surgery are not superior to those of early surgery. Ljunggren *et al.*[24] studying 219 patients, reported good recovery in 76% of patients undergoing late surgery (more than eight days after SAH) and in 74% of patients undergoing early surgery group (within 2.5 days of SAH). All patients were grade I–III (Hunt and Hess classification). The Cooperative Aneurysm Study, performed in 3521 aneurysm patients in 68 neurosurgical centres, showed that the incidence of rebleeding in patients operated upon within the first three days after SAH was lower (6%) than in patients operated upon 7 to 11 days after SAH (14%).[25] Although there was a reduction in the rebleeding rate after early surgery, the timing of operation did not influence the overall morbidity and mortality. However, in the North American Subset of the International Cooperative Study, the best results were obtained when surgery was performed within three days of SAH.[26] From 1980 through 1983, 772 (21.9% of total 3521 patients) patients admitted to 27 neurosurgical centers in the United States and Canada from days 0 to 3 after SAH were enrolled in the study. Overall outcome in patients planned for surgery on days 0–3 after SAH was equivalent in terms of mortality to patients planned for surgery on days 11–32 after SAH,

TABLE I Neurological grading system for patients with SAH

Grade	*Criteria*
Grade I	Asymptomatic or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion, or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis
Grade V	Deep coma, decerebrate rigidity, moribund appearance

From *Hunt WE, Hess RM.* Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968; 28: 14.

but early surgery showed improved recovery. Patients planned for surgery 7–10 days after SAH had nearly twice the mortality of other intervals. These results argue for early diagnosis and surgical intervention after SAH.

Cerebral vasospasm

In the past, rebleeding was considered to be one of the major causes of morbidity and mortality of SAH. Of 2265 patients admitted to the Cooperative Aneurysm Study, Kassell *et al.* reported that 4.1% of patients rebled during the first 24 hr after the initial haemorrhage. Rebleeding was documented by bloody spinal fluid or CT scanning. They concluded that rebleeding occurred most commonly during the first 24 hr with a cumulative rate of approximately 20% during the first two weeks after the initial SAH.[27] Recently, Kassell *et al.*[28] demonstrated that cerebral vasospasm following aneurysmal SAH was one of the most important causes of cerebral ischaemia and was the main cause of death and disability in patients with SAH. Vasospasm, especially of the severe and diffuse variety, was associated with a reduction in both regional CBF and $CMRO_2$.[14,17] Angiographic vasospasm is defined as a narrowing of the column of dye in the major cerebral arteries. The narrowing is time-dependent, rarely pronounced before the fourth day after the initial haemorrhage and reaches a peak at about the seventh day.[29-31] Clinical cerebral vasospasm, the syndrome of the ischaemic consequences of cerebral artery narrowing, is characterized by an insidious onset of confusion and decreased level of consciousness followed by focal motor and speech impairment and is often heralded by worsening headache and increasing blood pressure.[28] Cerebral arterial spasm, as revealed by angiography, is a major cause of delayed cerebral ischaemia.[32] Using positron emission tomography, Carpenter *et al.*[33] measured the regional $CMRO_2$, oxygen extraction fraction and CBF, and concluded that the initial aneurysm rupture produced a primary reduction in $CMRO_2$ and that subsequent vasospasm caused ischaemia.

Delayed cerebral ischaemia is the major cause of death and disability in patients with SAH. The treatment of cerebral vasospasm may be considered in the following categories: (1) prevention or reversal of the arterial narrowing, (2) prevention or reversal of the ischaemic neurological deficits, and (3) protection from infarction.[28] Direct pharmacological dilatation of spastic vessels has not been demonstrated but therapy may be directed to prevent its development or ameliorate the ischaemic consequences.[34-36] Several agents have been used to prevent or reverse the arterial narrowing. Calcium channel blocking agents have been used because the contraction of cerebral arterial smooth muscle cells is calcium-dependent and can be blocked by preventing the influx of extracellular calcium. Nimodipine has proved effective both in reducing the mortality rate and in diminishing the severity and incidence of permanent deficits caused by delayed ischaemic deterioration.[34,36-38]

Cerebral haemodynamics

Carbon dioxide reactivity

Cerebral arteries and arterioles react quickly to changes in $PaCO_2$. In the $PaCO_2$ range 25 to 60 mmHg the relationship between CBF and $PaCO_2$ is linear, with a flow change of about 4% per millimeter of mercury.[39] The vascular reactivity to carbon dioxide is considered to be the predominant factor in the regulation of regional CBF and seems to be a stable phenomenon. Even after severe head trauma or stroke, carbon dioxide reactivity is at least partially preserved,[40,41] but Schalén *et al.* reported that loss of carbon dioxide reactivity is a good predictor of outcome from head injury.[42] Reduction of cerebral blood flow by hyperventilation is used to control acute increase of intracranial pressure such as epidural haematoma. Voldby *et al.*[43] studied cerebral vasomotor reactivity to hypocapnia in 34 patients between the 3rd and 13th day after rupture of an intracranial aneurysm and reported that the cerebrovascular response to hyperventilation was generally preserved. Clinical grading of SAH (Hunt and Hess classification) correlates with the disturbance of carbon dioxide reactivity, autoregulation and intracranial pressure (Table II). In animals, Artru *et al.*[44] reported that carbon dioxide responsiveness was abolished during profound hypotension induced with trimet-

TABLE II ICP and vascular responsiveness after subarachnoid haemorrhage

Grade	*ICP mmHg)*	*CO_2 response $\Delta CBF/\Delta\ PCO_2$*	*Autoregulation $\Delta CBF/\Delta\%MABP$*
II	10 ± 3	1.61 ± 0.67	-0.042 ± 0.194
III	18 ± 6	1.02 ± 0.5	-0.230 ± 0.514
IV-V	29 ± 6	0.61 ± 0.42	-0.344 ± 0.219

Data are mean ± SD. Units for CO_2 response are ml · 100 g^{-1} · min^{-1} change in CBF· $mmHg^{-1}$ change in CO_2. Autoregulation is expressed as ml · 100 g^{-1} · min^{-1} change in CBF· % change in MAP (a value of 0.000 would be perfect autoregulation, and a more negative number indicates progresssive autoregulatory impairment.
From *Voldby B, Enevoldsen EM, Jensen FT.* Cerebrovascular reactivity in patients with ruptured intracranial aneurysm. J Neurosurg 1985; 62: 59, and *Voldby B, Enevoldsen EM.* Intracranial pressure changes following aneurysm rupture. Part I: clinical and angiographic correlations, J Neurosurg 1982; 56: 186.
And from *Todd MM, Warner DS.* Neuroanesthesia: a critical review. *In:* Rogers MC, Tinker JH, Covino BG, Longnecker DE (Eds.). Principles and Practice of Anesthesiology. Mosby Year Book 1992; 1633.

aphan or sodium nitroprusside. We evaluated carbon dioxide reactivity during deliberate hypotension induced by prostaglandin E_1 (PGE_1), nitroglycerin (TNG), nicardipine in patients during cerebral aneurysm surgery.[45-47] Nitroglycerin- or nicardipine-induced hypotension did not change carbon dioxide reactivity during hypotension in our studies.[46-47]

Autoregulation

Autoregulation protects the brain against ischaemia caused by decreased blood pressure. The exact mechanism of autoregulation is unknown but cerebral resistance vessels dilate in response to a decrease in arterial blood pressure or an increase in intracranial pressure.[2,48] Cerebral autoregulation is a vulnerable mechanism: impairment of autoregulation has been found in patients with SAH,[3,49-50] and brain tumour.[39] Severe head injury is accompanied by marked disturbances of autoregulation.[51] Loss of autoregulation often correlates with changes in cerebral blood flow in the resting condition with either hypo- or hyperperfusion.[52] In intracranial tumours, autoregulation is impaired in the diseased area and its surroundings.[53] After SAH, cerebral blood flow may be reduced in response to small decreases in blood pressure in patients with cerebral vasospasm. In the first week after SAH, a 10–20% reduction of mean arterial blood pressure using trimetaphan or sodium nitroprusside decreased CBF in patients with angiographic cerebral arterial vasospasm.[54] Using the intraarterial ^{133}Xenon injection method, Voldby *et al.*[43] studied the effects of hypotension on $CMRO_2$, $AVDO_2$, cerebral spinal fluid lactate and intraventricular pressure in 34 patients within first 13 days of SAH. Mean arterial blood pressure was reduced between 10 and 20% for five minutes by *iv* trimetaphan or sodium nitroprusside. The severity of angiographic cerebral vasospasm was measured by angiography immediately after the CBF study and there was a close correlation between the degree of cerebral vasospasm and the impairment of cerebral autoregulation, and patients with slight vasospasm and normal resting cerebral blood flow pattern frequently showed focal changes during induced hypotension. Diffuse severe vasospasm was accompanied by global impairment of autoregulation. There was a correlation between the presence of cerebral vasospasm and impaired autoregulation and between the degree, extension of vasospasm and the severity of autoregulatory impairment.

Cerebral blood flow

Several methods are available to measure CBF including ^{133}Xenon inhalation,[55] ^{133}Xenon clearance,[56-57] xenon computed tomographic blood flow mapping,[58] positron emission tomography,[59] and the hydrogen clearance technique.[60-61] Ishii[13] and Pickard *et al.*[62] reported that, after SAH, regional CBF was reduced by 25 and 50%, depending on the impairment of consciousness. Values for regional CBF below 20 but higher 12 ml · 100 g^{-1} · min^{-1} were associated with clinical neurological deficits that were reversible. The values for regional CBF of 12 ml · 100 g^{-1} · min^{-1} or less were associated with clinical deficits that were not reversible when the vasospasm resolved. Bell *et al.*[63] studied ischaemic cerebral oedema and regional cerebral blood flow in 41 baboons and reported that the threshold of ischaemia is 40.5% of normal cerebral blood flow in cortex and 34.4% of normal flow in subcortical white matter. They concluded that reversal of the neurological deficit and prevention of ischaemic oedema formation can be expected if cerebral blood flow can be restored to above the 40% threshold within 30 minutes. Their results suggest the risk of brain ischaemia during induced hypotension. In our studies, prostaglandin E_1 (PGE_1) did not change LCBF after the induction of hypotension.[45-46] Trimetaphan decreased LCBF at 30 minutes after the start of agent but increased to the pre-

treatment level after its discontinuation,[64] whereas nitroglycerin increased LCBF at 30 min after the start and decreased to the pretreatment level after its discontinuation.[46]

Cerebral metabolic rate (CMR) is the rate at which the brain used or produced metabolic substrates or by-products, oxygen ($CMRO_2$), glucose (CMR-Glu), or lactate (CMR-Lact). Cerebral metabolic rate plays a major role in the control of cerebral blood flow and is altered by anaesthetics.

Cerebral arterial blood flow velocity

The normal value of mean middle cerebral artery (MCA) blood flow velocity varies from 35 to 90 $cm \cdot sec^{-1}$ and an average value is about 60 $cm \cdot sec^{-1}$ during awake and resting states.[65] Elevation of mean MCA velocities >120 $cm \cdot sec^{-1}$ has been widely used as the criteria for vasospasm.[66,67] The degree of MCA velocity elevation has been correlated with the clinical symptom caused by delayed ischaemia.[66] A rapid increase of velocity may predict neurological deterioration, but high velocities are often unaccompanied by neurological symptoms.[66,68] Davis *et al.* compared serial arterial velocities and neurological deficits in 34 patients after SAH, and reported that eight of 16 patients without delayed ischaemia had evidence of vasospasm (MCA velocity >120 $cm \cdot sec^{-1}$).[69] They concluded that concordant vasospasm and hypoperfusion were most often present in patients with delayed ischaemia and lateralizing neurological deficits.

Induced hypotension during cerebral aneurysm surgery

Induced hypotension has been used during cerebral aneurysm surgery to reduce the risk of intraoperative aneurysmal rupture. Intraoperative rupture of a cerebral aneurysm dramatically interrupts a microsurgical procedure and jeopardizes the outcome for the patient. However, it is controversial whether induced hypotension is useful in the prevention and management of intraoperative aneurysmal rupture. Giannotta *et al.* performed a retrospective analysis in 276 consecutive surgical procedures for 317 intracranial aneurysms to determine the factors that governed the outcome from intraoperative rupture of aneurysms. There were 16 intraoperative aneurysmal ruptures in 108 operations without induced hypotension and 20 ruptures in 168 operations with hypotension, but in cases of induced hypotension, 11 of the 20 patients suffered from permanent deficits or died. However, all 16 patients of intraoperative ruptures without induced hypotension made a good recovery. They concluded that induced hypotension may not be necessary in the management of intraoperative rupture of aneurysm.[70] The major argument against induced hypotension is that SAH and cerebral vasospasm may disrupt cerebral autoregulation, especially in patients with low classification grade. The safety of systemic hypotension during cerebral aneurysm surgery depends on preservation of adequate CBF. Hitchcock *et al.* studied the outcome in 112 patients operated upon for clipping of intracranial aneurysms and concluded that the incidence of postoperative neurological deficits was higher in those patients subjected to intraoperative hypotension below 60 mmHg mean arterial blood pressure and the duration of hypotension.[71] The margin of safety is reduced during induced hypotension and therefore the technique should be used only when it may benefit the patient and only by those trained and experienced in its use.[5] The competency of cerebral autoregulation and CBF in aneurysm patients during hypotensive anaesthesia is variable. Considerable effort has been directed to determine the ideal drug for induced hypotension. The three drugs in the most common use are TNG, SNP and isoflurane, but there are no prospective studies demonstrating an improved neurologic outcome with any agents. Lam *et al.* performed a retrospective study in 85 patients receiving a combination of halothane (0.5–1%), fentanyl and SNP, and in 105 patients with isoflurane-induced hypotension. Outcome was evaluated as – good: complete recovery except for minor cranial nerve dysfunction; satisfactory: major focal neurological deficit; poor: vegetative state or death. They concluded that there were no differences in outcome between the hypotensive methods.[72]

Marked reduction in arterial pressure diminishes bleeding and on occasion allows the neurosurgeon to regain control of an irreversible situation but the neurological and systemic effects of severe hypotension coupled with extreme blood loss should be borne in mind, and normotension, normovolaemia, administration of cerebral protective agents, and appropriate temporary clipping can be utilized to minimize the risk of cerebral ischaemia.[73] Ausman *et al.*[74] concluded that it may be unreasonable to make the whole brain hypotensive when only the vessel with the aneurysm needs to be controlled and they recommended the use of temporary vascular clips. Although no clinical comparisons between induced hypotension and temporary vascular clipping have been done, there are some advantages to temporary vascular clipping. In patients with impaired cerebral autoregulation and decreased CBF after SAH, temporary vascular clipping may be safer than induced hypotension, because it decreases flow only to that portion of the brain supplied by the temporarily occluded vessels and maintains collateral flow, rather than decreasing CBF to the entire brain through induced hypotension.

Extreme intraoperative hypertension is one of the major problems during cerebral aneurysm surgery. The

treatment of hypertension in association with SAH is complicated in cases of cerebral vasospasm that may exacerbate fluctuations in CBF. It has been reported that antihypertensive therapy should be withheld except when elevations in blood pressure are extreme because the clear benefits have not been shown from reducing CBF.[75]

Hypotensive drugs

Prostaglandin E_1

The prostaglandins are a large family of naturally occurring substances with a variety of biological actions. Prostaglandin E_1 (PGE_1) reduces blood pressure by relaxing vascular smooth muscle, mainly by dilatation of resistance vessels, but in large doses may exert a predominant vasodilator action on the systemic arterial circulation so that it induces systemic hypotension.[76,77] In our study, PGE_1 (initial dose: 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused continuously to induced systemic hypotension, and PGE_1 did not change LCBF and carbon dioxide reactivity during surgery, but the hypotensive effects of PGE_1 persisted after its discontinuation.[45,46] Goto *et al.* also reported prolongation of the hypotensive effect during general anaesthesia, although the blood concentration of PGE_1 decreased to preadministration levels about ten minutes after the end of infusion.[78] Although PGE_1 inhibits platelet aggregation[79] Carlson reported that inhibition did not occur at clinically used doses of PGE_1.[80]

Sodium nitroprusside

Sodium nitroprusside (SNP) has been used to induce hypotension during cerebral surgery because it has a rapid onset and a short half-life. Its onset of action is within 30 sec, and peak hypotensive effect occurs within two minutes and hypotensive effect disappears within three minutes after its discontinuation. Sodium nitroprusside primarily dilates resistance vessels, and the haemodynamic response to its administration results from a combination of venous pooling and reduced arterial impedance. Sodium nitroprusside must be administered as a continuous infusion. The initial dose is 0.5–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and higher rates are necessary to induce hypotension during surgery. The adverse effects of SNP include cyanide and thiocynate toxicity, rebound hypertension, intracranial hypertension and blood coagulation abnormalities. The principal metabolite of nitroprusside, cyanide, is converted to thiocyanate in the liver and may accumulate in patients with liver disease. Accumulation of cyanide can occur if SNP is infused at rates greater than 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The risk of thiocynate toxicity increases when SNP is infused for more than 24 hr, especially if renal function is impaired. Toxic effects may be prevented or reversed by the administration of sodium nitrate, sodium thiosulphate, or hydroxycobalamin. The combination of SNP with captopril reduces the dose requirement of SNP.[81] Sodium nitroprusside markedly increases the intracranial pressure in patients with low intracranial compliance[82-83] and the effect is even greater than nitroglycerin.[84] Cerebral vasodilatation induced by SNP is unlikely to affect regional cerebral blood flow which remains unchanged during the hypotension and gross cerebral metabolic disturbance have not been observed.[85] Sodium nitroprusside may induce coagulation disturbances and SNP-induced coagulation abnormalities can induce increased bleeding caused by vasodilatation.[86] Cerebral perfusion is better maintained during drug-induced hypotension; of the drugs commonly used, perfusion is maintained best with SNP.[5] Cerebral blood flow is maintained during SNP-induced hypotension.[87] However, high organ blood flow alone may not guarantee adequate tissue oxygenation and this may be particularly relevant with SNP because it has no effect on $CMRO_2$.[88]

Adenosine

Adenosine is an endogenous vasodilatator and is involved in several vascular beds. It is normally salvaged from the tissue and rephosphorylated by ATP-dependent kinase reactions.[89-90] It has been used to induce hypotension in cerebral aneurysm surgery due to its rapid onset and stable hypotensive action without rebound hypertension, and its favourable cardiovascular effects[91,92] with only minor decreases in whole body oxygen consumption.[89] The effects of this agent are rapidly and spontaneously reversed when its administration is discontinued and it has no haematological or biochemical toxicity.[89] Lagerkranser *et al.* studied the effects of adenosine-induced hypotension on CBF, $CMRO_2$ and cerebral lactate production in ten patients undergoing cerebral aneurysm surgery and reported that adenosine-induced hypotension at MAP between 40–50 mmHg (5.3–6.7 kPa) did not cause any adverse effects on cerebral circulation or oxygenation.[93] Zäll *et al.*[94] reported that adenosine-induced hypotension during cerebral aneurysm surgery inhibits renin release and induces profound decreases in renal blood flow and glomerular filtration rate caused predominantly by afferent glomerular arterilar vasoconstriction. When the adenosine infusion was discontinued, glomerular filtration rate returned to baseline levels. These results suggest that its use should be limited to brief periods of hypotension, and it should not be used in patients with impaired renal function.

Nitroglycerin

Organic nitrates are polyesters of nitric acid, whereas organic nitrites are esters of nitrous acids. Nitrate esters are characterized by a sequence of carbon-oxygen-

nitrogen. On the other hand, nitro compounds possess carbon-nitrogen bonds. Organic nitrates, nitrites and several other compounds that are capable of conversion to nitric oxide have been termed nitro-vasodilators. Nitroglycerin (TNG) dilates both veins and arteries directly, and has little effect on the smaller resistance vessels of the body. Nitroglycerin's relaxation of vascular smooth muscles stems from the intracellular reaction of organic nitrates with a sulfydryl moiety on the nitrate receptor to form inorganic nitrite. Nitrite is then oxidized to form nitric oxide. Nitric oxide in combination with tissue thiols forms an activator of guanylate cyclase, the enzyme that catalyzes the formation of cyclic guanylic acid (cGMP) (Figure 3). The increase in cGMP with guanylate cyclase activator is associated with relaxation of vascular smooth muscle. Nitric oxide is thought to be the active intermediator for the action of this broad class of agents.[95-96]

Perioperatively, intravenous nitroglycerin infusion may be used to reduce blood pressure during cerebral aneurysm surgery. Cottrell studied the changes in intracranial pressure in hyperventilated patients undergoing craniotomy and reported that intracranial pressure increased from 14.2 to 30.8 mmHg and cerebral perfusion pressure decreased from 90.2 to 38.2 mmHg.[83] Low intracranial compliance contraindicates the use of TNG prior to dural opening. Langerkranser[97] reported that TNG may cause increased intracranial pressure, especially in patients with intracranial hypertension, by its venodilatating effects on the cerebral circulation and concluded that, during neurosurgical operations, the administration of TNG should, if possible, be restricted to the period when the dura is open, and the lungs should be moderately hyperventilated. Maktabi *et al.*[98] studied the effects of SNP-, TNG- and isoflurane-induced hypotensive anaesthesia on the cardiovascular system and intrapulmonary shunting in 30 patients and reported that cardiac index was decreased more by TNG and isoflurane than with SNP at a mean arterial blood pressure of 40 mmHg.

Trimetaphan

Trimetaphan (TMP) acts mainly by sympathetic ganglionic blockade as well as by histamine release.[99,100] A distinct advantage of TMP is that automatic reflexes are blocked. Knight *et al.* demonstrated that norepinephrine, epinephrine, plasma renin activity, and angiotensin II did not increase as much after TMP as after SNP.[101] Using a thermal gradient blood flow meter, we measured local cerebral blood flow in 19 patients undergoing cerebral aneurysm clipping during TMP-induced hypotension and found that local cerebral blood flow was reduced with TMP.[63] Turner *et al.* reported that TMP has little dilator action on the cerebral vessels, as indicated by the lack of increase in intracranial pressure with this drug.[102] Trimetaphan is rarely used because of the high incidence of adverse effects such as bowel and bladder atony and the rapid development of tachyphylaxis.

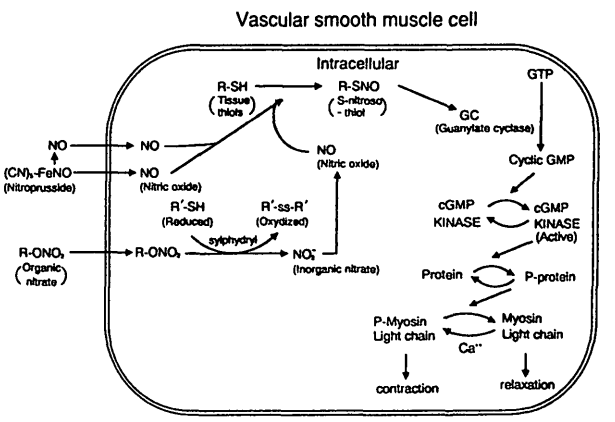

FIGURE 3 Schematic diagram of cellular mechanism of action of nitrogen oxide-containing vasodilators (nitrovasodilators). The conversion of guanosine triphosphate (GTP) is catalyzed by guanylate cyclase. Nitric oxide (NO) derived from the nitrovasodilators activates the soluble isoenzyme form of guanylate cyclase and results in increased cyclic guanylic acid (cGMP) synthesis and cyclic GMP dependent protein kinase activation. These events result in the dephosphorylation of myosin light chain and relaxation. From *Ignarro LJ, Lippton H, Edwards JC, et al.* J Pharmacol Exp Ther 1981; 218: 739, and *Murad F.* Cyclic guanosine monophosphate as a mediator of vasodilation. J Clin Invest 1986; 78: 3).

Calcium antagonists

The use of calcium channel blockers has enabled marked progress to be made in studies concerning the role of extracellular Ca^{++} influx in cardiac and smooth muscle contraction. Calcium channel blockers, structurally related to nifedipine, are beneficial in the treatment of hypertension, myocardial ischaemia, and cerebral and coronary vasospasm during anaesthesia.[103] The major antihypertensive mechanism of calcium antagonists is by decreasing systemic vascular resistance, modified by the counter-regulatory responses of the baroreflexes and the renin-angiotensin-aldosterone system.[104] However, the calcium channel blockers, verapamil[105] and diltiazem[106] may produce severe negative chronotropic and dromotropic effects when used to induce systemic hypotension. Recently, it has been shown that calcium channel blockers also affect the cerebral circulation. Nicardipine,[107,108] nimodipine,[109] verapamil[107] and diltiazem[110] increased cerebral blood flow in animals. Nicardipine is a water-soluble, photoresistant di-hydropyridine calcium channel blocker that causes potent systemic and coronary vasodilatation but does not result in negative inotropic, chronotropic, or dromotropic effects.[11] It has been reported that nicardipine increased cerebral blood flow in humans

and animals.[108,112] In our study, nicardipine did not change LCBF or carbon dioxide reactivity, but LCBF was improved in patients with good presurgical neurological status than in those with poor neurological status. The hypotensive effect of nicardipine persisted after its discontinuation which is similar to PGE_1[47] The elimination half-life of nicardipine increased to four to eight hours when a continuous intravenous infusion was administered.[112] Anaesthesia and operation may interfere with drug disposition, and lead to a decrease in systemic clearance and an increase in plasma concentration.[113] Consequently, the continuous administration of nicardipine to induce hypotension during anaesthesia may result in cumulative effects that persist after discontinuation of the infusion. It has been reported that the calcium antagonists dilate the cerebral resistance vessels and increase cerebral blood flow.[114]

Diltiazem is a benzothiazepine derivative calcium antagonist which acts by interfering with calcium-mediated events in excitation-contraction coupling in cardiac and smooth muscle. The effectiveness of diltiazem in patients with mild to moderate hypertension has been proved in double-blind comparison with placebo.[115,116] Also, diltiazem was effective when given intravenously to patients with hypertensive emergencies[117] and/or with postoperative hypertension.[118] Intravenous diltiazem has been used to prevent ischaemia in patients with coronary artery disease during non-cardiac surgery.[119] There is some information about the cerebral vascular effects of diltiazem which appears to block receptors and potential dependent calcium channels without blocking stretch-induced calcium influx.[120] It has been reported that diltiazem prevents or at least minimizes Ca^{++} entry into the vascular muscle and endothelial cells in the cerebral arteries through potential-sensitive and receptor-operated mechanisms, and that this effect has some selectivity for the cerebral arteries.[121]

Verapamil is a less potent vasodilator than nicardipine. Prompt reduction of blood pressure can be achieved after the intravenous administration of verapamil. The currently recommended dosage is 5 to 10 mg, given as an *iv* bolus over two minutes. Intravenous administration of verapamil causes a decrease in arterial blood pressure due to a decrease in vascular resistance, but the reflex tachycardia is blunted by the direct negative chronotropic effect of verapamil.[113]

Isoflurane

The volatile anaesthetic, isoflurane, has been used extensively to induce hypotension during cerebral aneurysm surgery because of its rapid onset of action, easy controllability, and rapid reversal of the cardiovascular effects on discontinuation. It causes peripheral vasodilatation with little effect on pulmonary gas exchange or cardiac output.[122,123] Newman *et al.* studied the effect of isoflurane-induced hypotension on CBF and $CMRO_2$ in 12 patients undergoing cerebral aneurysm surgery and concluded that, with regard to global cerebral oxygenation, isoflurane was a safe agent with which to induce hypotension.[88] Using thermal diffusion probe, Roth *et al.*[124] measured cerebral cortical blood flow and $CMRO_2$ in patients undergoing cerebral aneurysm surgery and concluded that CBF and oxygen delivery were maintained during isoflurane-induced hypotension during fentanyl-nitrous oxide anaesthesia. Haraldsted *et al.*[125] studying the cerebral arteriovenous O_2 difference during in 20 patients undergoing cerebral aneurysm surgery, concluded that cerebral blood flow and oxygen demand/supply ratios were maintained favourably during induction of hypotension with isoflurane at concentrations <2.5 MAC. Isoflurane causes an increase in intracranial pressure,[126] plasma epinephrine is decreased but plasma epinephrine and norepinephrine concentrations and plasma renin activity increased during induced hypotension in halothane-SNP combined group. It was concluded that isoflurane-induced hypotension with isoflurane anaesthesia, unlike SNP-induced hypotension with halothane anaesthesia, attenuated the stress response.[127] The role of the endothelium in the vascular response to volatile anaesthetics remains controversial. Several studies suggest that the volatile anaesthetics may induce endothelium-dependent relaxation in isolated vascular rings.[128,129] Stone *et al.* studied the endothelium-dependent vascular effects of isoflurane using isolated ring preparations of rat thoracic aorta and reported that isoflurane causes vasoconstriction through inhibition of basal EDRF production or stimulation of the release of an endothelium-derived vasoconstriction factor at low concentrations and that at higher concentrations a direct vasodilating effect of anaesthetic predominates.[129] However, the role of the endothelium in the vascular response to volatile anaesthetics remains uncertain.

Other vasodilators

HYDRALAZINE

Hydralazine causes direct relaxation of arteriolar smooth muscle and most of its effects are confined to the cardiovascular system. The decrease in blood pressure is associated with a decrease in vascular resistance in the coronary, cerebral and renal circulations. Hydralazine is well absorbed through the gastrointestinal tract and the half-life is one hour. Hydralazine is administered in doses of 20 to 40 mg *iv* when there is an urgent need to decrease blood pressure, but the response is very unpredictable and prolonged hypotension is not unusual even with doses

TABLE III Parenteral medications used in the treatment of hypertensive emergencies

Drug	*Administration**	*Onset*	*Duration of action*	*Dosage*	*Adverse effects and comments*
Sodium nitroprusside	*iv* infusion	Immediate	2–3 min	0.5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (initial dose, 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for eclampsia and renal insufficiency)	Hypotension, nausea, vomiting, apprehension. Risk of thiocyanate and cyanide toxicity is increased in renal and hepatic insufficiency, respectively; levels should be monitored. Must be shielded from light.
Diazoxide	*iv* bolus	1–5 min	6–12 hr	50–100 mg every 5–10 min, up to 600 mg	Hypotension, tachycardia, nausea, vomiting, fluid retension, hyperglycemia. May exacerbate myocardial ischemia, heart failure, or aortic dissection. May require concomitant use of a β-antagonist.
	iv infusion			10–30 $mg \cdot min^{-1}$	
Labetalol	*iv* bolus	5–10 min	3–6 hr	20–80 mg every 5–10 min, up to 300 mg	Hypotension, heart block, heart failure, bronchospasm, nausea, vomiting, scalp tingling, paradoxical pressor response. May not be effective in patients receiving α- or β-antagonists.
	iv infusion			0.52–2 $mg \cdot min^{-1}$	
Nitroglycerin	*iv* infusion	1–2 min	3–5 min	5–100 $\mu g \cdot min^{-1}$	Headache, nausea, vomiting. Tolerance may develop with prolonged use.
Trimetaphan	*iv* infusion	1–5 min	10 min	0.5–5 $mg \cdot min^{-1}$	Hypotension, urinary retention, ileus, respiratory arrest, mydriasis, cycloplegia, dry mouth. More effective if patient's head is elevated.
Hydralazine (for treatment of eclampsia)	*iv* bolus	10–20 min	3–6 hr	5–10 mg every 20 min (if no effect after 20 mg, try another agent)	Hypotension, fetal distress, tachycardia, headache, nausea, vomiting, local thrombo phlebitis; infusion site should be changed after 12 hr.
Nicardipine†	*iv* infusion	1–5 min	3–6 hr	5 $mg \cdot hr^{-1}$, increased by 1–2.5 $mg \cdot hr^{-1}$ every 15 min, up to 15 $mg \cdot hr^{-1}$	Hypotension, headache, tachycardia, nausea, vomiting.

**iv* denotes intravenous.
†Not yet approved by the Food and Drug Administration for this use.
From *Calhoun LA, Oparil S.* Treatment of hypertensive crisis. New Engl J Med 1990; 223: 1179.

as low as 10 mg. James *et al.* studied the effect of hydralazine-induced hypotension during enflurane anaesthesia in patients during neurosurgical operations, and reported that hydralazine is a simple, smooth, predictable, nontoxic technique to induce hypotension during neurovascular operations.[130]

DIAZOXIDE

Initially, diazoxide was developed as an oral antihypertensive drug, but it induced unacceptable side effects (hyperglycaemia, hypertrichosis). It was given parenterally for the treatment of hypertensive emergencies, but sodium nitroprusside has replaced diazoxide as the drug of choice for hypertensive cases. Although the plasma half-life of diazoxide is 20 to 60 hr, the duration of the hypotensive response is variable and can be as short as four hours or as long as 20 hr. The main indication for diazoxide is the treatment of hypertensive emergencies. However, excessive hypotension may induce cardiac or cerebral damage. The most common side effects caused by diazoxide are salt and water retention and hyperglycaemia.[131]

LABETALOL

Labetalol acts as a competitive antagonist at both α_1- and β_1-adrenergic receptors. The actions on both α_1 and β_1 adrenergic receptors induces a decrease in blood pressure in patients with hypertension. Orlowski *et al.* administered labetalol to 15 postoperative neurosurgical patients who had undergone neurovascular surgery. The patients had been treated initially with SNP to maintain reasonable arterial blood pressure, but because of excessive SNP dose requirements, intravenous labetalol was administered. Mean intracranial pressure decreased from 11.3 ± 6.1 mmHg with SNP to 8.6 ± 3.1 mmHg after conversion to labetalol.[132]

ESMOLOL

Esmolol is a selective β_1 antagonist with a very short duration of action and has a half-life of about eight minutes. It has been reported that esmolol and labetalol were useful in controlling systolic blood pressure in emergencies and in the recovery room in patients undergoing intracranial surgery[133] (Table III).

Clinical implications

The use of induced hypotension has declined because it may induce or exacerbate brain ischaemia during aneurysm surgery, but intraoperative rupture of a cerebral aneurysm, especially if rupture occurs before its exposure may induce catastrophic result. A recent retrospective study suggests the usefulness of temporal clipping than induced hypotension.[70] The use of temporal clipping to decompress aneurysms, or to treat intraoperative aneurysm rupture has been preferred to induced hypotension recently. However, it is unclear whether improvement in outcome results from the use of temporary clips or the increase in surgical experience and expertise.[134] Prolonged temporary occlusion can be unforgiving when the occluded vessel supplies numerous small perforators such as the carotid birfucation, the M1 segment of middle cerebral artery, or the anterior communicating artery. These arterial segments supply perforating vessels without collateral circulation. The other difficulty that arises from temporal clipping is the physical and anatomical limitations of applying multiple clips in a confined space, particularly with basilar aneurysms in which space is usually the limiting factor. Complete dissection of an aneurysm neck by surgical clipping and without injury to surrounding brain or blood vessels, is the goal of aneurysm surgery. In cases of giant cerebral aneurysm, fragile aneurysm or multiple cerebral aneurysms, induced hypotension may be recommended to prevent the intraoperative rupture, but long-term hypotension or profound hypotension may induce cerebral ischaemia after surgery and provoke end-organ ischaemia or infarction. Thus, profound and long-term hypotension should be avoided. During cerebral aneurysm surgery, the effect of vasodilators on cerebral vasculature should be kept in mind. Sodium nitroprusside, nitroglycerin and isoflurane have been recommended for induced hypotension because of their rapid onset and recovery and the stability of the cerebral vasculature.

Intraoperative hypertension during cerebral aneurysm surgery should be treated immediately because it may damage the cardiovascular, renal and central nervous systems and it may induce rebleeding and cerebral aneurysmal rupture during surgery. Any drug used for the treatment of intraoperative hypertension carries the risk of decreasing cerebral blood flow below the lower limit of autoregulation to induce cerebral ischaemia or infarction. Vasoactive drugs have less effects in the cerebral circulation than in other vascular beds, in part because of the protective effect of the blood-brain barrier, but drugs that penetrate the blood-brain barrier and dilate the cerebral vessels (e.g., hydralazine, sodium nitroprusside, nifedipine and verapamil) may lead to uneven cerebral perfusion due to an "intracranial steal" effect, and drugs that dilate cerebral vessels and increase cerebral blood flow may also cause an immediate increase in intracranial pressure and create the potential for cerebral herniation.[135]

In our studies, arterial blood pressure was reduced immediately after the start of hypotensive drugs, but the hypotensive effect of PGE_1 and nicardipine infusion persisted after their discontinuation. PGE_1 and nicardipine do not change LCBF; trimetaphan decreases LCBF and nitroglycerine increases LCBF. We confirmed that PGE_1, TMP, TNG and nicardipine did not change carbon dioxide reactivity during surgery but carbon dioxide reactivity had a close correlation with presurgical neurological status.

Conclusion

Induced hypotension has been used to decrease the risk of intraoperative aneurysmal rupture but the use of it is declining because of brain ischaemia. But intraoperative hypertension should be treated immediately to reduce the risk of rebleeding. Profound hypotension should be avoided. A drug that does not change CBF during cerebral aneurysm surgery should be used to induce hypotension.

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