RICHARDSON LECTURE

Protection of the Brain After Aneurysmal Rupture

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ABSTRACT: The majority of patients survive the first dangerous hours after an aneurysmal rupture. However, many subsequently succumb as a result of a variety of lethal complications. The most important of these develop as sequelae of the initial ischemia, rebleeding and the delayed onset of vasospasm. Some of these deleterious cascades can be aborted. Since the delayed complications such as vasospastic infarction can be accurately predicted, this is one of rare "strokes" that can have pharmacological pre-treatment. The natural history of rebleeding and vasospasm are described as well as their effects on blood flow, oxygen delivery and metabolism. Strategies to ameliorate acute and delayed ischemia and hypoxia are discussed. Finally, potential pharmacotherapies are detailed.

RÉSUMÉ: Protection du cerveau après rupture d'un anévrisme. La majorité des patients survivent aux premières heures qui sont dangereuses après la rupture d'un anévrisme. Cependant, plusieurs succombent ultérieurement à des complications létales variées. Les plus importantes de ces complications sont des séquelles de l'ischémie initiale, d'un saignement subséquent et d'une installation tardive d'un vasospasme. Certaines de ces cascades délétères peuvent être avortées. Des complications tardives tel l'infarctus vasospastique peuvent être prédites avec précision. Il s'agit donc d'une des formes rares d'accident vasculaire cérébral pour lequel un pré-traitement pharmacologique est possible. Nous décrivons l'histoire naturelle du ressaignement et du vasospasme ainsi que leurs effets sur le flot sanguin, la perfusion en oxygène et le métabolisme. Nous décrivons également des stratégies pour améliorer l'ischémie et l'hypoxie aiguës et tardives, ainsi que la pharmacothérapie.

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Aneurysmal Rupture

1. Ischemia

By a variety of mechanisms a rupture of a cerebral aneurysm can cause both global and focal ischemia. Global ischemia can occur at the time of initial rupture during which the intracranial pressure can rapidly reach that of mean arterial pressure with cessation of forward blood flow during the seconds to few minutes in which hemostasis in the aneurysmal rent occurs. Focal ischemia occurs later on and may be due to vessel distortion due to hematoma, edematous brain or distended ventricles. Early vessel occlusion is from extension of an intra-aneurysmal clot through the lumen of the vessel bearing the aneurysm, arterial dissection and iatrogenic arterial occlusion either at angiography or surgery. The most common cause of focal ischemia, however, is delayed arterial vasospasm resulting from the breakdown or periadventitial blood clot in the subarachnoid space. Of all types of ischemic stroke, this one is unique in that it is to some extent predictable, preventable and treatable. The involvement of endarteries uniquely supplying cerebral regions can result in a core of dense ischemia surrounded by a penumbra of brain between the normally perfused and non-perfused tissues. A greater or lesser portion of this ischemic, but not yet infarcted brain, has a potential for recovery under favorable circumstances.

2. Natural History

The outcome from aneurysmal rupture is frequently determined in the first few critical moments. Relevant prognostic factors include the volume of blood leaving the aneurysmal tear, the location of the bleeding (intracerebral, intraventricular, subarachnoid, subdural, or intra-aneurysmal), the number of bleeding episodes, the development of acute and chronic hydrocephalus as well as delayed cerebral vasospasm. These pathological factors are reflected by the neurological grade of the patient. Survival also relates to the age of the patient and the general state of health. Significant longstanding hypertension is an adverse factor. The closer the time to the bleeding, the higher is the anticipated mortality for each clinical grade. The location, size and complexity of the aneurysm as well as the experience of the surgical operator and his anesthetic and intensive care colleagues likewise influence overall management survival. The natural history for patients following aneurysm rupture is approximately one quarter dead by the second day, half by the

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second week and two thirds by the second month. The deaths within the first few minutes are usually due to global ischemia and cardiac arrest, deaths within the first few hours and days are more likely due to rebleeding than other causes, deaths towards the end of the first week and in the second week after the hemorrhage are often due to infarction from vasospasm. Later deaths are most frequently due to general medical complications. Medical and nursing aspects of the treatment of aneurysm patients are complex and demanding.[1-4]

3. Rebleeding

A major aim in protecting the brain after the initial hemorrhage is to prevent rebleeding. The factors which predispose to rebleeding in the first couple of weeks include a poor initial neurologic grade (because this results from a larger volume hemorrhage and consequently a bigger hole in the aneurysm), a shorter interval to the hemorrhage (the risks probably decrease over hours as well as days), advanced age, moderate to severe hypertension, female gender, rapid reduction of intracranial pressure by lumbar puncture, ventriculostomy or osmotic diuretics, intubation without adequate anesthesia and/or sedation.

A major advance in recent decades is the realization that early surgery can be performed safely in most cases and it is the definitive means of preventing destructive and fatal rebleeding.[5-7]

VASOSPASM

1. Vasospasm and Infarction

The vasoconstriction that results from the disintegration of organized blood clots around the adventitia of cerebral arteries is unlike that in systemic arteries because of the time interval to develop, steady increase and decrease, and the devastating symptomatology resulting from its presence. The development of ischemic infarction from cerebral vasospasm is unique amongst various types of stroke because it is predictable by the large amount of subarachnoid clot on the initial computed tomographic (CT) scan and unusual onset prior to 4 days after the hemorrhage, so that it is possible to pretreat, or treat very early, patients who are at risk. We should aim to institute therapy within a few minutes or hours of the development of symptoms and signs. Pharmacological agents may therefore prove more efficacious in this form of stroke than in most others which do not occur under medical observation.

The literature on cerebral vasospasm has been documented in a series of symposia and recent reviews.[8-16] Several recent monographs have also addressed the general subject of ischemic infarction.[17-22]

2. Prognostic Indicators

Factors which are associated with an increased risk of delayed ischemia from vasospasm include large volume initial subarachnoid hemorrhage, the time interval of 4-14 days post rupture, dehydration, the employment of antifibrinolytic agents, arterial hypotension, prolonged anesthesia with arterial hypotension and retractor compression, increased intracranial pressure, poor cardiac output, arrhythmias, anemia and hypoxia.

3. Incidence

The incidence of vasospasm depends on the timing of angiography in relationship to the day of hemorrhage as well as the experience of the angiographer. The observation of an internal carotid or middle cerebral artery which is 50% or less in diameter than the opposite side is generally interpreted as being severe spasm. The effect of spasm is, of course, also determined by its extent and the number of arteries involved. If angiography is performed around the peak time for vasospasm it will almost always be present to some degree in patients who had neurologic deficits at presentation (i.e. large volume subarachnoid clots). About one third of aneurysm patients will develop cerebral infarction entirely or partly due to vasospasm. In the last decade or so, most series reported death rates from vasospasm alone or in concert with other factors of between 5 and 15%. In the absence of any specific new therapy this improvement is probably due to a better management of fluid status and blood pressure. Severe diffuse spasm, involving the basal arteries only, occurs in about half the cases. In the other half there may be involvement of more distal sylvian or cortical vessels. Only very rarely will there be spasm only in the smaller cortical vessels. This probably reflects the relative distribution of the thicker subarachnoid clots.

4. Systemic Changes

The systemic signs of vasospasm include elevated temperature and white blood cell count (WBC). A plateau type fever above 38°C developed between days 5 and 12 in 88% of cases with severe vasospasm and delayed ischemia in one series.[23] In another series, if the admission temperature was above 37.5°C, 40% of the patients got vasospasm as opposed to 30% with a temperature below this. Average initial temperature was 36.4°C, rising to 37.8°C on day 5 in this large group of aneurysm patients.[24] If the admission WBC is more than 15 x 10^9/L, 40% of cases got vasospasm as opposed to 30% with an initial WBC count below this. Elevation of temperature has a rough correlation with degree of cerebral infarction.[25]

5. CT Findings

The CT scan has become a sensitive means of following the development of infarction due to vasospasm as well as predicting it. Of patients with high density clot in multiple cisterns on the initial CT scan, about 80% will subsequently get angiographic vasospasm if the angiogram is performed at the appropriate time. If there is severe vasospasm in the delayed angiogram, as many as 70% of patients will develop some evidence of infarction on the CT scan. A permanent delayed onset neurologic deficit is more likely if one entire carotid system plus the contralateral anterior cerebral arterial system is involved in severe spasm. More than 95% patients with ruptured aneurysms will show CT evidence of clot if studied in the first 24 hours. This drops to about 50% at the end of the first week and 30% at the end of the second week following the bleed. If there is minimal evidence of a CT clot in the study performed in the first 24 hours, the chance of the patient developing significant vasospasm is probably under 5%. The infarcts from vasospasm vary in shape and may be sharply delineated or not. Between 5 and 10% become hemorrhagic, usually 2 or 3 weeks after the bleed.[26]

6. Etiology

Blood in the cerebrospinal fluid is undoubtedly the cause of vasospasm. It is unclear which component(s) are responsible. There could well be complex interaction between the cellular elements including most importantly erythrocytes, with leukocytes

and platelets as well as proteins, lipids, carbohydrates, amino acids, electrolytes, vitamins, hormones, nitrogen break down products, blood gases and minerals. The factors in this complex process not only include blood in the subarachnoid space, but the response of the involved tissues including vascular endothelium, smooth muscle cells, vascular extracellular matrix, adventitia as well as the perivascular neural network. In addition, the reaction of the spinal fluid and brain may well be important.

It is currently considered that oxyhemoglobin is probably the source of the main spasminogen or spasminogens.[27] The time course of its release from disintegrating erythrocytes in the subarachnoid space or *in vitro* fits in with the time course of vasospasm. It can attack vascular smooth muscle membrane, increasing the permeability to calcium, stimulate free radical release, and cause the vascular smooth muscle membrane to become "leaky" to electric current. It appears to generate the destructive free radical OH^- in a similar fashion to H_2O_2 and Fe^{2+}. Hemoglobin is the principle protein contituent in the cytoplasm of mature erythrocytes and has a molecular weight of 68,000 daltons. It is composed of two dissimilar polypeptide chains (globins). Each globin attaches covalently to a tetrapyrrole called heme. Heme consists of a ferrous iron bound to a protoporphyrin XI. The average life span in the circulation is 120 days for erythrocytes and 15% break up in the blood, in which case hemoglobin is scavenged by the protein haptoglobin. Some hemoglobin breaks into globin and the heme, which is scavenged by the protein hemopexin. Most sensescent erythrocytes are scavenged by engulfing macrophages. The life span of an erythrocyte is dramatically altered in the cerebrospinal fluid compared to blood and most erythrocytes disintegrate and are engulfed by two or three weeks following the subarachnoid hemorrhage. When hemoglobin breaks down it produces globin and heme. Globin is broken into its constituent amino acids. The heme is broken down into iron and the linear tetrapyrrol, biliverdin. Biliverdin ultimately produces bilirubin through intracellular mechanisms and bilirubin in plasma is bound to albumin. Other smaller reaction products may also be vasoactive.

7. Transcranial Doppler Studies

If the transcranial Doppler velocities in the middle cerebral artery do not exceed 140 cm/sec, it is highly unlikely that infarction will occur, whereas infarction is likely if velocities exceed 200 cm/sec.[28] This is by no means foolproof, however, and a rapid rate of change in the velocity rather than absolute values may indicate impending vasospastic ischemia. Angiography remains the gold standard. If intracranial pressure is raised for whatever reason, the velocities may be spuriously decreased.[29] It is also not as accurate a means of judging ischemia as techniques such as Positron Emission Tomographic (PET) scanning or XeCT-Cerebral Blood Flow (CBF) studies, but the portability, safety and repeatability make it a useful adjunct to clinical judgement. Transcranial Doppler has been a moderately useful advance, although its limitations are becoming more evident.[30]

Oxygen and Aneurysmal Rupture

In preserving the flow of nutrients to the brain, we have to be concerned with both the ventilatory and circulatory pumps of the body. The pressure of oxygen presented to the circulating blood and its hemoglobin concentration will determine the content of oxygen which in conjunction with the degree of blood flow ultimately fixes the supply of oxygen available to the brain. Blood flow is dependent on blood pressure and the pumping efficiency of the heart. Work per unit time of the heart for normal oxygen transport is minimal at a hematocrit of 40%. It is greatly increased at a hematocrit less than 30 or above 55.

The cerebral metabolic rate for oxygen ($CMRO_2$) is depressed in the early phases of subarachnoid hemorrhage and the oxygen extraction fraction at that point is maintained normal. In the period of vasospasm beyond day 4, CBF falls in most studies and in order to maintain the $CMRO_2$ constant, oxygen extraction fraction has to increase. Another compensatory mechanism, interparenchymal vasodilation, results in an increase in cerebral blood volume. If infarction develops, then the metabolic rate for oxygen, the oxygen extraction fraction and the cerebral blood flow all fall in the affected region.

The normal $CMRO_2$ is 5 ml/100 g/min. Neural and electrical activity are abolished and infarction occurs when $CMRO_2$ falls below 1.5-1.7 ml/100 g/min. Deprivation of oxygen is the first ischemic metabolic parameter change to affect brain function because of the extreme dependence of membrane ionic potenitals on oxygen-dependent energy metabolism. Ischemia severe enough to cause persistent loss of membrane potential between 5 minutes and an hour, kills some but not all of the vulnerable neurons in the affected vascular territory. Beyond an hour, infarction begins in the central region of lowest regional CBF and circumferentially enlarges towards its maximal volume over 3-4 hours in rodents, and 6-8 hours in non-human primates. Attempts to attenuate the volume of infarct via pharmacological and other means depend critically on the time during which therapy is initiated and completed in relation to the onset and duration of ischemia.

Neuronal dysfunction and death begin when blood pressure falls below 40 mmHg or PaO_2 is less than 50 mmHg. This threshold is reflected in a $CMRO_2$ less than 1.5 ml/100 g/min or a cerebral metabolic rate for glucose less than 2 mg/100 g/min. A total absence of CBF for 6 minutes at normothermia leads to irreversible loss of brain. A regional blood flow under 20 ml/100 g/min is associated with hemiplegia.

There is no doubt that reducing the hematocrit and thereby the blood viscocity will result in an increase in CBF in most circumstances. However, the oxygen delivery to the brain may not be increased thereby. In the study by Hino and colleagues,[33] when they induced hemodilution (by phlebotomy 450 ml and rheomacrodex intravenously 500 ml) the hematocrit fell from 43 to 37% and the CBF increased from 45 to 48 simultaneously, but the oxygen delivery to the brain actually fell (CBF x total oxygen content of arterial blood = ml/100 ml/min = 8.7 to 8.0). It is clearly impractical to perform PET studies in a serial manner on every patient who has had a ruptured aneurysm, but it is important to bear in mind the possibility that elevating the CBF might not necessarily be beneficial under certain circumstances. The evidence for benefit from induced hypervolemia and hypertension in the clinical setting, although anecdotal and not verified by randomized trials, is still stronger than for hemodilution.

The effect of hematocrit reduction on oxygen delivery, even to non-ischemic brain is not definitely established. Kusunoki et al.[34] suggested that O_2 delivery was optimal at a hematocrit of 42%.

Every effort must be made to reduce pain and anxiety following aneurysmal ruptures since these factors can accelerate by 20 or 30% cerebral requirements for oxygen uptake.

Cerebral Ischemia

1. Biochemical Changes

Cerebral ischemia is a hemodynamic insult in which CBF is reduced sufficiently to cause neuronal damage. Global ischemia refers to equal reduction in flow through all blood vessels going to the brain, whereas focal ischemia is reduction in the flow in a branch or branches distal to the circle of Willis.

The threshold for reduced flow to produce edema is similar to that resulting in electrical failure (20 ml/100g/min), which is higher than that which produces complete energy failure. Cytotoxic edema is an early feature in ischemia and results from the movement of protein-poor fluid into the cells. Osmolality increases during ischemia because of the production of osmoles from lactate. Osmosis results in a net increase in tissue water content. With prolonged ischemia the blood brain barrier is damaged and serum protein is extravasated into the extracellular space resulting in vasogenic edema.

Ischemia principally reduces cerebral metabolism by interfering with substrate supply. Complete ischemia results in an isoelectric EEG within 30 seconds. Ischemia of a lesser degree however, might permit some ongoing metabolism and continued EEG activity. In such cases it is thought that drugs such as barbiturates might be helpful since they can reduce the cerebral metabolic rate by 50% or so. The drugs would then eliminate the electrical activity underlying the EEG. This would thereby decrease the demand for substrates. This might explain why barbiturates have been found to be protective in focal ischemia, but not in global. Hypothermia can provide greater protection than barbiturates since it can reduce the metabolic rate beyond the 50% level, below the point where the EEG is isoelectric.

The pathogenesis of ischemic infarction involves the reduction of regional cerebral blood flow due to vascular and hematologic events. Ischemia induces alteration in cellular chemistry which ultimately results in brain necrosis. Factors involved can include: cell signalling (neurotransmitters, neuromodulators), signal transduction (receptors, ion channels, second messengers, phosphorylation reactions), metabolism (carbohydrate, protein, fatty acid, free radicals), gene regulation and expression. These processes may be up or down regulated and are potentially reversible or irreversible in a time-dependent fashion.

Intracellular Ca^{2+} balance is maintained by Ca^{2+} influx and efflux through voltage sensitive and receptor operated channels and by membrane ATPase and by Na^+ - Ca^{2+} membrane exchangers.[35,36] Cytosolic Ca^{2+} levels also depend on binding by intracellular proteins such as calmodulin and the functioning of Ca^{2+}/Na^+ exchangers in mitochondrial membranes and the sequestration of Ca^{2+} in the endoplasmic reticulum. Factors responsible for the extension of the central infarct into the surrounding penumbral zone at risk include acidosis, edema, K^+/Ca^{2+} transients and altered protein synthesis. The fall in cellular adenosine triphosphate (ATP) leads to membrane and cytoskeletal breakdown, intracellular accumulation of Ca^{2+}, Na^+, Cl^- and H_2O as well as the production of metabolic acids resulting in intra- and extracellular acidosis. As ATP is depleted the Ca^{2+} pumps stop functioning and cytosolic Ca^{2+} levels rise. Ischemia interferes with the intracellular sequestration and binding of Ca^{2+}. As oxygen and glucose delivery falters, there is increased anaerobic glycolysis. This adverse metabolic development is enhanced by rising intracellular Ca^{2+} and progressive reduction in ATP production. Free radicals may also be involved in acute ischemic damage. Ischemia triggers increased activity by lipases, proteases, nucleases and by impaired protein phosphorylation which ultimately affects protein synthesis and gene expression. In severe ischemia resulting from cardiac arrest or middle cerebral artery acute occlusion, Ca^{2+} pumping out of the cell stops and entry is enhanced by the release of excitatory amino acids. Acidosis promotes edema formation by promoting Na^+ and Cl^- accumulation intracellularly, via coupled Na^+/H^+ and Cl^-/HCO_3^- exchange. It may also involve failure of H^+ extrusion. Post ischemic acidosis can trigger gross edema and cell lysis. Ischemia also results in the release of free radicals which can cause dysfunction of the microvasculature and damage to the blood brain barrier.

Many lines of experimental evidence have suggested that the elevation of intracellular calcium plays a critical role in the pathophysiology of ischemic neuronal death. Maintenance of the normal extracellular: intracellular Ca^{2+} ratio of 10,000:1 is due to a complex and tightly regulated system which requires a constant supply of energy.

In moderate ischemia of several hours duration, there may be partial preservation of energy dependent mechanisms continuing to regulate intracellular calcium although synaptic transmission is suppressed with attendant EEG silence. The energy normally spent restoring membrane ion gradients, which is dissipated during synaptic activity, plus the saving in energy resulting from reduced anaerobic synthesis of ATP, may maintain a near normal tissue energy status despite the ischemia. Increased K^+ conductance hyperpolarizes membranes, thereby reducing neurotransmitter release and responsiveness to them. Blockade of glutamate (NMDA or AMPA) channels which inhibit Ca^{2+} movement, can reduce infarct volumes to focal ischemia in certain animal models.

Eukaryotic cells subject to stress alter their genomic priorities so that protein synthesis is restricted to "heat shock" or "stress proteins". In focal ischemia in rats, CBF of 15-25 ml/100 g/min produces isoelectric modification of several proteins and induces synthesis of others. The P70 protein is a member of a highly conserved class of stress proteins which may have homeostatic funtions since it is produced in ischemic stress.[37]

2. Cerebral Blood Flow

Subarachnoid hemorrhage can cause an acute increase in intracranial pressure with a resultant acute decrease in global CBF followed by a reactive increase in cerebral blood flow if survival has occurred and flow was restored. Subarachnoid blood can result in metabolic depression of the cortex with a decrease in the cerebral metabolic rate and subsequent decrease in linked cerebral blood flow. Vasospasm can result in a regional reduction in CBF.

In the most severe type of aneurysmal rupture when the intracranial pressure equals mean arterial pressure for many minutes, global ischemia exists and beyond a certain point "no-reflow" will occur even if the circulation is artificially resumed and maintained. Presumably under such circumstances, there is swelling of vascular elements, including the endothelium and

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perivascular glia, increased blood viscosity, decreased local perfusion pressure, arterial spasm and occlusion. The duration of lack of blood flow to the brain which will result in no-reflow is probably around 6 or 7 minutes when there is complete ischemia at normothermia. The duration for incomplete ischemia to result in no-reflow probably is a function of the volume of brain involved, the vascular anatomy and the way in which flow is restored. It is unlikely that restoration of flow in the middle cerebral artery after 4-6 hours will result in tissue recovery and prevention of infarction. The therapies to obviate the disastrous consequences of global ischemia have included drugs to reduce vascular tone, methods of improving blood rheology, reduction of the oxygen and glucose requirements of the tissue and various pharmacological therapies. None of the foregoing have been successful, except in certain experimental paradigms. Cell dysfunction progressively occurs when CBF falls below the normal 50 ml/100 g/min. When flow approaches 50% of this there occur electrolyte shifts, tissue acidosis, edema, and inhibition of protein synthesis, all of which are potentially reversible until flow reaches less than 20% of normal at which point dissipative ion fluxes, which are time-dependent, usually result in cell death. Observable changes in the brain electrical activity begin around CBF 30-40 ml/100 g/min, and proceed to electrical silence around 15 ml/100 g/min. Spontaneous neuronal activity falls off rapidly at this lower level. Simultaneously the Ca^{2+} levels rise sharply as does the intracellular ratio of Na^{+}/K^{+}. Tissue adenosine, GABA and glutamate all rise sharply at these levels and then fall.[38] The problem with many of these biochemical changes is that they occur within seconds or minutes of the onset of cessation of blood flow, so it is little wonder that incremental brain damage can occur through a variety of mechanisms following the initial aneurysmal rupture.

CBF is maintained constant at a mean blood pressure of 60-130 (200/110) in normotensive patients. Vasodilators can exacerbate the damage to the blood brain barrier and aggravate cerebral edema from hypertension through mechanisms such as acidosis, hypercapnia and small vessel dilatation. When the mean blood pressure is raised more than 50 mmHg above normal, the regional CBF in ischemic zones may be paradoxically decreased. Cerebral blood flow is maintained fairly constant through a wide range of physiological blood pressures (autoregulation), but CBF can be increased by exceeding the upper end of the curve to the right, so that in a given patient it is important to monitor the blood flow by the neurologic examination or direct recording techniques if one is manipulating blood pressure in a therapeutic attempt. The most potent influences on blood flow are the levels of carbon dioxide and oxygen. Curiously little attention has been paid to hypercarbia in modern times as a potential way of restoring normal flow. This is because of a perceived adverse effect of tissue acidosis and intracranial hypertension resulting from increased cerebral blood volume. None the less, it seems important to avoid extremes of hypocapnia in situations where the brain is already suffering from borderline ischemia. At P_aCO_2 40 mm/Hg, an increase in CBF of 4% occurs for each increase of 1 mmHg. An acute increase in P_aCO_2 is countered by a chronic increase in the CSF HCO_3 which normalizes the CSF pH in 24-36 hours. A reduction in P_aO_2 only causes vasodilatation at less than 50 mmHg.

Potential therapeutic techniques that have been investigated for cerebral ischemia include methods to improve regional blood flow, enhance substrate delivery and alter ischemic thresholds. Blood flow can be favourably influenced by hypertension, hypervolemia, reduction in viscosity, vasodilatation, prevention of edema, reperfusion and angioplasty. The ischemic threshold has been modified by hypothermia, barbiturates, etomidate, calcium channel blockers, drugs to prevent cytotoxicity, and free radical scavengers.

3. Barbiturate Protection

Barbiturates remain one of the most attractive class of agents to protect the brain during temporary focal ischemia.[39] Provided there is ongoing focal electrical activity they can reduce it and concurrently the cerebral metabolic rate and oxygen consumption. As a result, CBF and cerebral blood volume diminish. There is a concomitant reduction in intracranial pressure. The circulatory changes continue until electro-cerebral silence is obtained and the cerebral metabolic rate is approximately halved.[40] In several primate models treatment with barbiturates was protective, in a dose related fashion, if given prior to the onset of focal cerebral ischemia. It has not been as clearly established whether or not they are effective if given after an ischemic process is established, particularly if the ischemia is permanent. It is conceivable that the protection noted in the earlier experiments was due to a slight, but significant, fall in brain temperature. Pentothal was very popular initially, but this waned when serious cardiovascular depression associated with high dosage was noted. Long duration of action may inhibit collateral flow. Its prolonged activity may interfere with post-anesthetic recovery and neurologic assessment.

Etomidate is a non-barbiturate drug capable of inducing similar cerebral metabolic suppression without the significant cardiac side effects. Etomidate-induced burst suppression was utilized in the busy aneurysm service at Dallas beginning in the early 1980's. Doses of 0.4 - 0.5 mg/kg were used to achieve burst suppression prior to temporary clip application. Temporary clipping for up to 60 minutes was performed without evidence of infarction. These surgeons have been favourably impressed by the speedy recovery from anesthesia and the apparent protection afforded. Their current regimen is a 1.0 mg/kg loading dose followed by an infusion of 10 mg/kg/min to maintain burst suppression until the temporary clips are removed.

4. Mild Hypothermia

Another area in which ischemia can be predicted and pretreatment begun in the aneurysm patient is when there is deliberate occlusion of aneurysm bearing vessels during the final dissection and clip placement. Projecting from animal experiments, I now deliberately let the patient's temperature drift down to around 34 degrees hoping for the neuronal protection afforded by even this small drop in brain temperature. Cold irrigation is employed rather than body temperature irrigating fluid. Mannitol, which in addition to being an osmotic diuretic can act as a free radical scavenger, is given as a bolus just prior to the placement of temporary clips. Finally, an attempt is made to raise the blood pressure prior to clip application, thereby improving collateral flow. It is routinely possible to have temporary clips in place for ten to fifteen minutes without evidence of neurological deficit or infarction. Also, extrapolating from animal experiments, we should avoid the use of glucose solutions pre- and intraoperatively.

Prevention of Ischemia

1. Timing

Infarct volumes can be reduced in a variable fashion experimentally, depending on the time at which therapy is given in relation to the onset of ischemia. At the border of the infarct EEG silence is interspersed with anoxic depolarizations. The physical dimensions of the ischemic penumbra are inversely related to the steepness of a gradient between normally and non-perfused brain. Cerebral protection involves therapy prior to the ischemic insult in contradistinction to resuscitation which refers to interventions instituted after the onset of the ischemia. Treatment begun more than 6 - 8 hours after the onset of infarction in human beings is very likely to be ineffective and for that reason it is vital to begin promptly any therapeutic maneuvers in patients who develop late onset speech difficulty, hemiparesis or decrease in consciousness more than three or four days after aneurysmal rupture. Concurrent with efforts to elevate the cardiac output, blood volume and blood pressure, should be efforts to rule out coexisting space occupying lesions, anoxia and electrolyte abnormalities.

2. Preventing Rebleeding

When a patient is first admitted the major initial threat to his life is rebleeding, so that hypertension should be rapidly brought under control by analgesics and antihypertensive agents prior to enduring the initial angiogram. In the period from four or five days following the bleed, assuming the aneurysm has been clipped, no attempt should be made to lower the blood pressure, since hypertension may be a homeostatic mechanism developing in the face of vasospasm. Antifibrinolytic drugs (e.g. Amicar) may have a role if there is little subarachnoid clot and early surgery is impossible.

3. Preventing Infarction

Focal ischemic infarction from vasospasm can be prevented more or less by the improvement in CBF which comes from optimizing cardiac output, induction of hypervolemia and hypertension, prevention of cardiac arrhythmias and normalization of intracranial pressure. Oxygen delivery can be improved by giving oxygen by mask or through an endotracheal tube with a ventilator. Anemia should be avoided. The lumens of accessible severely spastic arteries can be enlarged by angioplasty and possibly to a lesser extent by the use of intraarterial papaverine. "L-type" Ca^{2+} channels can be blocked by dihydropyridines, such as nimodipine. Their use has been associated with better outcomes in the setting of aneurysmal rupture. Theoretical free radical scavengers such as mannitol may be helpful. There have been recent suggestions that the inhibition of Fe^{2+}-dependent lipid peroxidation by 21 amino-steroids may be efficacious and this is currently being subjected to clinical trial. Initial animal experimental results suggest that endothelin antagonists might also be helpful.

In those cases having delayed referral, in whom vasospasm is already established (usually day 4 – 12), it is particularly important to avoid hypotension and dehydration. Early surgery is probably advisable with immediate postoperative balloon angioplasty plus or minus the use of intra-arterial vasodilators.

It is important to deny access by addicted patients in the post-bleeding period to cigarettes or cocaine. Smoking can exacerbate vasospasm. Cocaine-induced hypertension can precipitate re-rupture.

The postoperative complications following early surgical intervention include hemorrhage and infection, vasospasm, general medical complications (pulmonary, cardiac, electrolyte, deep vein thrombosis and embolization, gastrointestinal), seizures, delayed hydrocephalus, rebleeding from residual aneurysm and associated or new vascular normalities.

Treatment strategies for focal ischemia in the setting of ruptured aneurysm should involve a prompt start (a delay of 6 – 8 hours after the onset of hemiplegia is likely to be insurmountable), then must be maintained for days to protect against recurrent ischemia in slowly evolving and long lasting vasospasm. Newer protective therapy should be simultaneously given with measures to improve CBF and oxygen delivery. Since the bulk of any infarct is unresponsive to therapeutic measures these should be directed towards prolonging penumbral survival during the vasospastic interval.

Vasospasm may be prevented by early surgery and mechanical removal of subarachnoid clot. The instillation of intrathecal t-PA in open trials was associated with reduction in clinically significant vasospasm in cases at high risk and a randomized trial is underway.[42-43]

Early surgery has the advantage of permitting the early definitive management of associated hemorrhages as well as those in a subarachnoid location. The removal of subdural hematomas and intracerebral hematomas can be carried out by direct surgical aspiration. Findlay and colleagues,[44] used t-PA intra-ventricularly for aneurysmal intraventricular hemorrhage. In eight aneurysm cases (six anterior communicating, two pericallosal) six were grade IV and two grade V. A solution of 1 mg t-PA/1 ml sterile water was given in doses of up to 1 – 4 mg per injection through ventricular catheters. Equivalent amounts of CSF were withdrawn prior to the instillation. Immediately after the instillation the tubing was clamped for an hour or so and then drained at low pressure. This can result in excellent blood clearance much faster than would occur normally. There is the added advantage of maintaining catheter patency to permit monitoring of the intracranial pressure and sampling of the ventricular fluid.[44]

While not proven efficacious by prospective, randomized trial, anecdotal cases provide dramatic evidence of efficacy of balloon angioplasty in dilating spastic vessels.[45] Considerable judgement is involved in deciding when to use this modality since it is not entirely without risk. If employed too late it can result in conversion of a bland to a hemorrhagic infarction.

Intraarterial papaverine is normally given through catheters placed as close to the affected arterial system as possible. As much as 300 mg/vessel is injected over one to several hours. The effect may last as long as 24 to 36 hours, but it is often short-lasting. It can temporarily improve the diameters of the anterior cerebral arteries which are difficult to reach by balloon dilating catheters. Possible adverse side effects include hypotension and elevated intracranial pressure. Means of controlling these would be in place prior to the instillation.

4. Fluid Management, Blood Pressure and Cardiac Output

The preferred solutions for hypervolemic hemodilution and the treatment of cerebral ischemia from vasospasm include albumin (25 or 5%) 1 – 1.5 g/kg/day divided in 4 – 6 doses/day, each

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administered over 30 – 60 minutes: stored or packed frozen plasma, one or two units (150 – 200 ml. each) every 4 – 6 hours; packed red cells (when hemoglobin is less than 10 gm/dl and hematocrit less than 30%) and crystalloid solutions such as 0.9% sodium chloride or Ringers lactate at 100 – 150 ml/hour.

Cardiac output should be optimized in the patient who is developing ischemic symptoms.[47] The lowest pulmonary artery wedge pressure for maximum cardiac output should be sought. For some patients this pressure may be in the range of 12 – 14 mmHg and the employment of higher pressures around 18 or 20 may pose an increased hazard of symptomatic pulmonary edema. We are not certain what the optimal hematocrit is for a patient threatened with focal cerebral ischemia. Many of the early studies looking at this question were performed on neurologically normal patients. In dogs (whose normal hematocrit is 50%) studies by Lee et al.,[48] suggested that a hematocrit of 30% is optimal, this is obviously not directly transferable to humans.

Shimoda et al.,[49] found a 35% incidence of delayed ischemia, hypervolemic therapy was used in 84%, this included a reduction in hematocrit to 30% and a pulmonary capillary wedge pressure of 13. In the cases treated with deliberate hypervolemia, 46% developed infarction and fully 28% had some complication of the hypervolemic therapy. The problems were most commonly cerebral edema and hemorrhagic infarction. If cerebral edema increased after the hypervolemic therapy 78% of their patients died. They suggested that such therapy not be employed if the patient was more than six days out from their hemorrhage and if they already showed established edema on the CT scan.

Extreme hemodilution may be harmful in patients with symptomatic vasospasm according to Hashimoto and coworkers.[50] In 165 cases operated in the first seven days, 15% got CT infarction, 2% got CT hemorrhagic infarction and 7% got brain swelling. The 6% of cases with reversible clinical vasospasm had a mean hematocrit of 35.8%, the 12% with progression to CT infarction had values of 31.2%.

I personally prefer induced hypertension and hypervolemia to hemodilution. My initial drug of choice for raising the blood pressure in the face of clinical deterioration attributable to vasospasm is dopamine 2 – 20 μg/kg/min. The rate of delivery is titrated against the blood pressure and neurologic response. Dopamine-induced hypertension is associated with increased CBF after aneurysmal SAH. Such changes however, are not always directly related to hypertension and there is a potential for inducing ischemia as well so that ongoing observation is essential.[51]

Levy and colleagues,[52] suggested that if delayed ischemic deficit is refractory to hypervolemia that the β-agonist dobutamine should be considered. They simultaneously employed .5 – 1L 5% albumin and 150 cc. of lactated Ringer in solution in association with 5 – 10 μg/kg/min and simultaneously reduced the peripheral resistance. In 160 SAH cases they experienced a 34% incidence of delayed ischemic neurologic deficit. 40% got better with hypervolemia alone. In 23 such cases refractory to increased blood volume 78% improved with dobutamine. They achieved a 5% increase in cardiac index with 11% increase in blood pressure. The cardiac index is not reliably reflected by the central venous pressure. In their experience a pulmonary artery wedge pressure of 14mmHg was associated with maximal cardiac performance.

Hypervolemic hemodilution can be hazardous in the setting of established cerebral edema and infarction, cardiogenic or neurogenic pulmonary edema, adult respiratory distress syndrome, increased intracranial pressure and moderate to severe anemia (hematocrit less than 30%). The undesirable side effects of hypervolemic hemodilution include decreased oxygen carrying capacity, aggravation of cerebral edema, pulmonary edema and anemia. One must always balance the necessity of optimizing the circulation with the known complications of intensive care efforts. These include, but are not limited to infection from intubations and lines, drug reactions including anaphylaxis, allergies, hypotension, pulmonary edema, organ toxicity, anemia from excessive sampling, tracheal stenosis from prolonged intubation, injury to the heart, vessels and nerves, venous thromboembolism and non-specific adverse effects of sleep deprivation and stress.[53]

5. Normoglycemia

Glucose levels above 120 mg/dl in the first 72 hours post-SAH were associated with 46% poor outcomes, whereas lower levels had 30% poor outcomes, corresponding death rates were 20% and 7%.[54] High glucose levels during the first week also predicted a poor outcome. In a rat model, insulin administered pre-ischemia, which induced normal to moderate hypoglycemia improved survival and reduced neurologic deficit as opposed to the results in animals getting high dose insulin or placebo.[55] While it is known that elevated glucose concentrations prior to an ischemic insult can increase the adverse histologic effects, it is not clear whether reducing glucose levels after the onset of ischemia is helpful or not.[56] It is probably reasonable to strive for normal range glucose levels in patients following aneurysmal rupture.

6. Current Pharmacotherapy

In randomized controlled trials of nimodipine treatment after subarachnoid hemorrhage, in seven series of 1284 cases deaths and poor results were reduced by 31%. There were 646 patients in six series studied after proven aneurysmal subarachnoid hemorrhage and deaths and poor results were reduced by 36%. Nimodipine treatment is therefore begun as soon as possible after admission, although there have not been clear cut demonstrations of its efficacy in preventing vasospasm which was the reason is was originally employed in human trials.[57] A similar drug, Nicardipine, appears to be more effective in antagonizing vasospasm, but overall improved outcome was not observed.[58] A calcium channel blocker developed in Japan, AT877, was apparently efficacious in preventing vasospasm and infarction in one randomized clinical trial.[59]

Various pharmacological approaches have proven effective in neural protection in experimental ischemia produced in animals in vitro[60] and in vivo,[61] particularly those with smaller brains. To date there have been no strikingly successful transfers of this knowledge to the human arena. The explanation for this is complex. To begin with it is frequently possible to treat experimental animals prior to the ischemic insult or shortly thereafter. This proves very difficult with humans suffering from ischemic stroke.[62,63] One of the opportunities posed by the ruptured aneurysm case is that we can anticipate the onset of delayed ischemia so that prophylactic therapy is uniquely possible in this type of stroke.

Potential Therapies

1. 21-aminosteroids

These agents inhibit iron-dependent lipid peroxidation. They were beneficial in some animal SAH models. In preliminary clinical trials certain dosages have been associated with very low post-operative mortality. Further studies are warranted.

2. Endothelin Antagonists

The most potent constrictor of vascular smooth muscle is the polypeptide endothelin, so a role in the genesis of vasospasm has been postulated.[64,65] There are endothelin receptors in vascular smooth muscle of different types. Endothelin is produced in significant amounts by vascular endothelium, but other cells such as vascular smooth muscle cells can also produce it. Very low concentrations of endothelin which do not produce vasoconstriction by themselves can increase this response to other agents. Oxyhemoglobin stimulates the production of endothelin by endothelium and vascular smooth muscle cells.[66] Endothelin inhibits the production of endothelial derived vasodilating agents (eg. nitric oxide). It is possible that endothelin plays a role in the multifactorial genesis of cerebral vasospasm. Antithrombin II, arginine vasopressin, transforming growth factor-β, and thrombin can all increase the synthesis of big endothelin-1 in endothelial cells. By the action of converting enzyme, big endothelin-1 is changed into endothelin-1. This reacts with the endothelin A receptor on vascular smooth muscle triggering contraction. There are being developed currently anti-endothelin compounds which block one or more of the different types of endothelin receptors (a, b, or c).

3. Vasodilators

Nitric oxide may well be the endothelial derived relaxing substance. It is generated from L-arginine by nitric oxide synthase within the endothelium. Vasodilators such as nitroprusside can increase the amount of nitric oxide in the target cells. Nitric oxide synthase antagonists such as L-NMMA have the opposite effect. Nitric oxide, by cGMP independent mechanisms, can increase the amount of GMP available to bring about vascular smooth muscle dilation.

4. Glutamate Antagonists

The amino acid glutamate is a fast excitatory transmitter in brain. If its concentration is pathologically high however, it can kill neurons. It may be a key factor in damage resulting from ischemia. Blockade of its synaptic transmission or the utilization of specific antagonists of post-synaptic glutamate receptors may protect central neurons against hypoxia and ischemia.[67-71] Glutamate may cause early cell death by electrolyte movements of sodium and chloride which induce water shifts with resultant cell lysis. The delayed toxicity to glutamate is possibly mediated by Ca^{2+} influx. The draw-back in application of glutamate blocking agents has been that currently available ones are active only at high concentrations, cross the blood brain barrier poorly and potentially antagonize normal glutamate transmission which may be essential to vital functions. The theory of excitotoxicity is based on the selective vulnerability of certain regions of the brain to ischemic insults (CA1 sector in the hippocampus) and the fact that such regions tend to have a rich glutaminergic innervation. In addition, delayed neuronal necrosis develops in a time locked fashion following an ischemic insult. In some models the concentration of excitatory amino acid glutamate goes up with the institution of recirculation following ischemia. Amino acid glutamate receptors are named after their selective excitors: kainate, NMDA, AMPA (q), aminophosphonobuterates. Excitatory transmission can be inhibited by baclofen and other agents. A total blockade of excitatory neurotransmission might induce a requirement for total support of respiration and cardiovascular function.

As a result of a variety of brain insults such as ischemia, trauma and seizures, the excitory amino acids (glutamate, aspartine) are released and depolarize the post-synaptic membrane. There follows a cascade of events which result in cellular edema, Ca^{2+} influx to the intracellular space, failure of membrane homeostasis and ultimately cell death, the post-synaptic hyperpolarization and metabolic inhibition by inhibitory amino acids (GABA agonists) may be protective.

In some animal experiments glutamate receptor antagonists have prevented focal ischemic neuronal death. In the rabbit, cortical injury has been reduced by dextromethorphine and dextrophan. MK 801 has reduced evidence of hippocampal (CA 1) injury and improved survival in gerbil models and reduced evidence of cortical injury in the cat. These agents are usually more effective in vitro than in vivo. MK 801 does not prevent neural injury in transient global ischemia. As yet these agents have not found application in the prevention of focal ischemia in ruptured aneurysm cases. Unfortunately many antagonists of the excitotoxic amino acid glutamate which protect neurons in culture and in animal models have had unacceptable side effects in humans.

5. Leukocyte Adherence Inhibitors

Recently there has been evidence that leukocytes may be important in the initiation of infarction through rheological effects or direct participation in thrombosis.[72] Polymorphonuclear leukocytes and monocytes adhere to vascular endothelium through complex receptor-ligand interactions. Anti-adhesion antibodies have been applied in an attempt to reduce blood vessel blockage by leukocytes. This remains a field of intense investigation, but there are no clinically applicable drugs available at the present.

6. Perfluorocarbons

Perfluorocarbons were initially disappointing as a means of reducing viscosity and increasing oxygen delivery to ischemic tissue. A new agent, fluoromethaloadamantane has small particle size, low viscosity and high perfluorocarbon content.[73] In a rabbit model of acute ischemia its use was associated with a smaller infarct size than in controls. Previous perfluorocarbons had adverse affects on immune and hematologic systems. Further studies of these newer agents are indicated. They may have incorporated within them antioxidants and free-radical scavengers, to help overcome problems related to reperfusion.

Conclusions

The following statements now seem to be reasonably proven: surgical treatment is better than the natural history for ruptured aneurysms, very early surgery is better than a policy of waiting in all but apparently moribund patients or extraordinarily difficult lesions, definitive clipping is superior to all other types of treatment for ruptured aneurysms, antifibrinolytics have no significant role and hypotension and dehydration as therapeutic maneuvers should be abandoned. There are many practical measures which can now be taken to obviate the development of clinically significant vasospasm. These include early surgery to definitively prevent rebleeding and providing an opportunity to mechanically remove as much blood as possible from the basal cisterns. In addition, catheters can be placed in the ventricles or subarachnoid space for the injection of tissue plasminogen activator which facilitates the dissolution of clot in the basal

cisterns. During surgery the body can be cooled by several degrees through simple measures. It is likely that this has a protective effect by analogy to carefully controlled animal studies. Mannitol has the advantage of being used for brain shrinkage as well as the theoretical possibility that it acts as a free radical scavenger during temporary vascular occlusion intra-operatively. The use of metabolic depressants such as the barbiturates and etomidate has not found general favor, but it may be reasonable to employ them in certain circumstances. The use of nimodipine has apparently been associated with a reduction in infarction rates. Careful attention must be paid throughout the hospital course to avoiding hypotension, hypovolemia, fever and hyperglycemia. Many other therapeutic approaches are theoretically attractive to protect the brain from ischemia, but await a more detailed knowledge of the pathophysiology and clinical trials.

The devastation resulting from the initial effect of aneurysmal rupture is beyond our control. About all that can be done is to seek out aneurysms in populations at special risk and clip them prophylactically. Much however can be done to halt the ischemic cascades that inevitably follow the initial hemorrhage, thereby protecting the brain.

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