Brain Ischemia in Patients with Intracranial Hemorrhage: Pathophysiological Reasoning for Aggressive Diagnostic Management

DANIEL NARANJO¹, MICHAL ARKUSZEWSKI², WOJCIECH RUDZINSKI³,
ELIAS R. MELHEM¹, JAROSLAW KREJZA¹

¹Department of Diagnostic Radiology of the University of Maryland, Division of Clinical Research; Baltimore, Maryland, USA

²Department of Neurology, Medical University of Silesia, Central University Hospital; Katowice, Poland

³Department of Cardiology, Robert Packer Hospital; Sayre, Pennsylvania USA

Key words: brain ischemia, cerebral ischemia, cerebral hemodynamics, cerebral blood flow, subarachnoid hemorrhage, cerebral vasospasm, cerebral emboli, cerebral perfusion review

SUMMARY – *Patients with intracranial hemorrhage have to be managed aggressively to avoid or minimize secondary brain damage due to ischemia, which contributes to high morbidity and mortality. The risk of brain ischemia, however, is not the same in every patient. The risk of complications associated with an aggressive prophylactic therapy in patients with a low risk of brain ischemia can outweigh the benefits of therapy. Accurate and timely identification of patients at highest risk is a diagnostic challenge. Despite the availability of many diagnostic tools, stroke is common in this population, mostly because the pathogenesis of stroke is frequently multifactorial whereas diagnosticians tend to focus on one or two risk factors. The pathophysiological mechanisms of brain ischemia in patients with intracranial hemorrhage are not yet fully elucidated and there are several important areas of ongoing research. Therefore, this review describes physiological and pathophysiological aspects associated with the development of brain ischemia such as the mechanism of oxygen and carbon dioxide effects on the cerebrovascular system, neurovascular coupling and respiratory and cardiovascular factors influencing cerebral hemodynamics. Consequently, we review investigations of cerebral blood flow disturbances relevant to various hemodynamic states associated with high intracranial pressure, cerebral embolism, and cerebral vasospasm along with current treatment options.*

Introduction

Insufficient blood supply of oxygen and/or energy to the brain causes stroke with subsequent significant physical and cognitive disability or death. A sudden embolic occlusion of a major cerebral artery can cause an acute stroke because there is typically not enough compensatory blood supply via collateral pathways, whereas in case of slowly progressing atherosclerotic narrowing of a large carotid or cerebral artery, collateral vessels can develop and provide a compensatory perfusion to the affected vascular territory. In patients with chronic ischemia; stroke can occur if the blood supply via the narrowed vessel and collaterals

is further compromised by an event such as a hypotensive episode, occlusion of the already narrowed vessel, or further progression of the stenosis.

The mechanism of stroke after intracranial hemorrhage seems to be more complex because several additional factors can affect cerebral hemodynamics right after the ictus. The term “stroke”, however, always indicates infarct of neuronal tissue regardless of the primary cause, either ischemic or hemorrhagic, and size of infarcted volume of the tissue. Survivors of spontaneous rupture of a vessel due to an aneurysm arteriovenous malformations (AVMs), or head trauma are at high risk of stroke because of the development of disturbances to cerebral

hemodynamics and/or brain oxygenation. In these patients timely prediction and detection of dangerous hemodynamic states that can lead to stroke are crucial to implement more aggressive preventive therapy. The goal of this review is to outline of those aspects of cerebrovascular physiology and pathophysiology that are pertinent to hemodynamic disturbances in patients after intracranial hemorrhage.

Physiological aspects of cerebral blood flow regulation

Brain tissue constantly maintains an extremely high metabolic rate. Cerebral oxygen consumption (≈ 3.5 ml/100g tissue/min)¹ accounts for about 20% resting total body oxygen consumption. The metabolic demand must be matched by high blood flow supply, which on average exceeds 50 ml/100g tissue/min, accounting for 15-20% of the total cardiac output^{1,2}. As the brain almost exclusively uses glucose for its energy utilisation and in general does not store energy, continuous blood supply, maintained within a narrow range, is absolutely required for brain function (90%) and cell viability (10%)³. Cerebral blood flow (CBF) is driven by cerebral perfusion pressure (CPP), represented by the difference between mean arterial blood pressure (ABP) and intracranial pressure (ICP), working in concert with cerebrovascular impedance. The components which make up cerebrovascular impedance include: 1) cerebrovascular resistance (CVR), which is inversely proportional to the forth power of the vessel radius when laminar flow occurs and the flow is in steady state; 2) the internal fluid resistance, which depends on viscoelastic properties of arterial walls, viscosity of the blood and flow velocity; 3) blood inductance, which is dependent on its rheostatic properties and momentum; 4) vascular compliance, which is related to the elasticity of the vessel wall^{4,5}. Alteration of any of the components, which make up impedance in a non-steady state system, such as occurs in the cerebrovascular system, can significantly impact the blood flow. Microvascular constriction most significantly increases the impedance⁶. *The ability of brain microvasculature to maintain cerebral blood flow relatively constant despite wide variations in CPP is called "cerebral autoregulation" (CA)*. In the normal state, CA maintains relatively constant CBF within the range of mean ABP from about 60 to 150 mm Hg⁷. *However, the upper and lower*

limits of CA are not fixed and can be shifted up or down by endogenous as well as exogenous factors. Sympathetic nervous system activity and increased levels of angiotensin II, for example, shift the upper and lower limits of CA up towards higher pressures, while chronic use of antihypertensive medications have the opposite effects^{8,9}. Patients with untreated hypertension have limits of regulation set on a higher level than healthy people⁸. This is important because in these patients overzealous antihypertensive treatment may lead to a dangerous reduction of CBF at relatively high ABP. Mechanisms of CA are complex and not fully understood. *It is surmised from the results of numerous experimental studies that CA is maintained by three different control pathways: vasogenic, metabolic and neurogenic*.

The vasogenic mechanism is based on the intrinsic ability of cerebral vessels to respond to changes in shear stress and transluminal pressure¹⁰. Increase in transluminal pressure activates vascular smooth muscle cells of the arterial wall leading to a decrease in the diameter of arteries^{11,12}. On the other hand, contraction of cerebral vessels increases vascular wall shear stress¹³. This triggers endothelial cells to release factors that relax vascular smooth muscles and dilate vessels¹². These counteracting mechanisms assure optimal adjustment of the vessel diameter to CPP at any time.

The exact mechanisms of vascular contraction in response to increases in transluminal pressure remain unclear. It appears, however, that mechanical dilation of smooth muscle cells in the arterial wall leads to activation of phospholipase C (PLC)¹⁴. Increased PLC activity leads to elevated diacylglycerol levels, activating protein kinase C, which is known to activate nonselective cation channels, depolarizing the smooth muscle membrane potential and enhancing calcium entry through voltage-dependent calcium channels. Increased concentration of free calcium ions activates the myosin light chain kinase, which phosphorylates myosin light chains and causes muscle contraction¹⁵. It is also possible that stretching of muscle cells directly activates calcium channels and leads to increased calcium concentration without activation of the PLC-dependent pathway¹⁶. Contrary to intraluminal pressure-induced contraction, which seems to be dependent only on smooth muscle cells, shear stress-induced vasodilation requires the interaction of endothelial cells and vascular muscles. Synthesis of nitric oxide (NO) is necessary for this phenomenon to occur¹⁷.

Shear stress increases the activity of endothelial nitric synthase (eNOS) and causes release of NO, which diffuses to adjacent smooth muscle cells and induces vasodilation through activation of potassium channels in those cells^{18,19}. Shear stress may also directly increase the expression of eNOS, as a shear stress-response element has been found in the promoter region of the gene for eNOS²⁰. It is not clear how significant a role the vasogenic mechanism plays in maintaining and regulating CBF and whether it depends somehow on the caliber of the cerebral arteries involved.

In *metabolic* regulation, arterial resistance is modified by waste products of energy metabolism (CO₂), partial pressure of O₂, and release of specific vasoactive substances such as adenosine and potassium ions from neurons in response to insufficient blood supply. The most important metabolic factor is tension of CO₂ in the periarteriolar space, although CVR is not directly affected by the CO₂ tension. It is the accompanying shift in periarteriolar pH, which regulates diameter of cerebral vessels²¹. Hypercapnia and the resulting decrease in extracellular pH cause cerebral vasodilation and increase in CBF, while hypocapnia leads to cerebral vasoconstriction and CBF decrease. Mechanisms responsible for regulation of CVR by CO₂ tension and accompanying pH changes are not clear. Hydrogen ions may directly activate potassium channels in smooth muscle cells leading to its hyperpolarization or they may induce a release of vasodilatory prostaglandins, adenosine or NO from neurons, glia or vessels²²⁻²⁶. Hypoxia, potassium ions and adenosine also lead to hyperpolarization of smooth muscle cells and consequently dilation of cerebral vessels. It appears that hypoxia-induced vasodilation is mediated by activation of potassium channels, while increased concentration of potassium ions in extracellular fluid activates electrogenic Na/K pumps and smooth muscle inward rectifier potassium channels^{27,28}. Adenosine acts on cerebral vessels through its receptors located in arterial smooth muscle membrane²⁹. Activation of these receptors leads to opening of calcium-dependent and ATP-dependent potassium channels^{30,31}.

While there is a consensus that vasogenic and metabolic mechanisms play critical role in regulation of cerebrovascular tone, the importance of *neurogenic* regulation in the control of CBF is still a matter of debate. The cerebral vessels are innervated by extrinsic and intrinsic systems of nerve fibers. The “extrinsic” sys-

tem refers to nerve fibers originating in ganglia belonging to sympathetic, parasympathetic and sensory ganglia, while nerves originating within the brain represent an “intrinsic” system³². Activation of sympathetic vascular nerves leads mainly to release of norepinephrine and neuropeptide Y³³. *Sympathetic stimulation constricts large cerebral arteries. However, CBF does not decrease, because the constriction of large cerebral vessels is immediately compensated for by dilation of resistance arterioles*³⁴. The role of sympathetic innervation seems to be related to protecting the brain against ABP increases through the mechanism of sympathetic activation shifting the upper and lower limits of CA towards higher pressures. *Parasympathetic vascular nerve fibers release vasoactive intestinal polypeptide, acetylcholine and NO*^{35,36}. *Activation of these nerves causes cerebrovascular dilation, the physiological significance of which is still not clear*³⁷. Fibers originating in sensory ganglia contain calcitonin gene-related peptide, substance P, neurokinin A and pituitary adenylate cyclase-activating polypeptide^{38,39}. These fibers cause dilation of cerebral vessels and their physiological role appears to be a counteracting action of cerebral vasoconstrictors⁴⁰. Activation of these fibers may contribute to an increase in CBF occurring in pathologic conditions such as meningitis, and may play a role in pathogenesis of migraine^{41,42}.

Vascular fibers belonging to the intrinsic system originate in different parts of the brain such as nucleus basalis, locus coeruleus and raphe nucleus⁴³⁻⁴⁵. These fibers may modulate vascular tone directly or through stimulation of perivascular interneurons and glial cells^{46,47}. Activity of the intrinsic system may decrease or increase local blood flow depending on the rostrocaudal level of activation of their cells of origin within the brain. The physiological significance of this system is not yet completely elucidated^{44,45}.

*For academic purposes, CBF regulation is parceled into several major mechanisms, though the division is somehow artificial. The mechanisms influence and modify each other at any given time and the overall cerebrovascular tone is the product of interplay of many processes. It is clear that some of these mechanisms share a common biochemical pathway at the level of vascular muscle cells. For instance vascular dilation caused by parasympathetic activation, shear stress and hypercapnia, at least in part, is mediated by the same factor – NO*⁴⁸.

Neurovascular coupling

The brain's information-processing capacity is limited by the amount of oxygen and energy available. When neurons are active, blood flow in that local brain region increases to meet the enhanced local metabolic demand⁴⁹. *The tight coupling between neuronal activity and blood flow is known as "neurovascular coupling". This phenomenon seems to be dependent on both astrocytes and perivascular neurons.*

Increased local neural activity leads to release of glutamate acting on astrocytic metabotropic glutamate receptors⁵⁰. Activation of glutamate astrocytic receptors leads to increased synthesis of arachidonic acid, which is metabolized to vasodilatory prostanoids like prostaglandin E2 (PGE2) and epoxyeicosotrienoic acid (EET)^{51,52}. PGE2 and EET diffuse to vascular muscle cells and dilate vessels increasing local blood flow^{51,52}. However, during this process a significant amount of arachidonic acid reaches vascular muscles as well. Smooth muscle cells contain enzymes (CYP4A), which generate powerful vasoconstrictor 20-hydroxyeicosotetraenoic acid (20-HETE) counteracting PGE2 and EET-induced vasodilation^{47,53}. The question arises, what shifts this balance towards vasodilation? Glutamate released into the synaptic space activates postsynaptic NMDA-type glutamate receptors located on perivascular neurons^{54,55}. This leads to activation of neuronal NO synthase and production of NO, which reaches smooth muscle cells. NO not only exerts vasodilatory effects but also binds to the heme moiety of CYP4A enzyme and inactivates it, thereby preventing further synthesis of 20-HETE from arachidonic acid^{56,57}. Thus activation of both nNOS positive neurons and astrocytes seems to be necessary for proper functioning of neurovascular coupling. It is likely that astrocyte-derived vasodilatory prostanoids are direct mediators while neuronal NO acts as a modulator of this process.

Respiratory and cardiovascular factors and cerebral hemodynamics

Both oxygen and CO₂ tension have powerful effects on the cardiovascular system through the peripheral and central chemoreceptors. Peripheral chemoreceptors are located in the aorta and internal carotid artery and respond to both hypoxemia and hypercapnia. The peripheral chemoreflex causes hyperventilation, transiently activates sympathetic traffic to peripheral blood vessels, and increases vagal activity

to the heart⁵⁸. Activation of peripheral chemoreceptors does not change CBF⁵⁹. Central chemoreceptors are located in the ventrolateral medulla and detect pH changes in the interstitial fluid⁶⁰. Activation of the central chemoreceptor reflex causes hyperventilation and increased sympathetic stimulation to the vasculature. Changes in sympathetic tone have a limited effect on CBF at normal PaCO₂ levels⁶¹. However, the sympathetic nervous system seems to attenuate the CO₂-induced increase in CBF. This phenomenon may indicate a moderate direct effect of the sympathetic nervous system on the cerebral vasculature⁶¹. *Sympathetic stimulation can have more important effects on segmental vascular resistance and cerebral microvascular pressure in pathologic conditions. Generalized increases in the sympathetic discharge, causing substantial increases in ABP, can prevent concomitant increases in CBF by acting on both small resistance and large vessels*^{34,62}.

The arterial baroreceptor reflex, which plays an integral role in regulating peripheral vascular tone and heart rate in response to changes in ABP, seems to have no impact on the CBF. Neither interruption nor stimulation of baroreceptor nerves affects CBF or CVR at ABP within the range of CA^{63,64}. However, cerebral vasoconstriction occurs in healthy humans during graded reductions in central blood volume. The magnitude of this response is small compared with changes in systemic vascular resistance⁶⁵. *It seems that this degree of cerebral vasoconstriction is not by itself sufficient to cause syncope during orthostatic stress, but can exacerbate the decrease in CBF associated with hypotension if hemodynamic instability develops.*

Cerebral ischemia and investigations of cerebral blood flow disturbances

Cerebral infarction occurs when blood supply is not sufficient to support cellular viability or when a low nutrient supply induces apoptosis. *Death is a complex function resulting from a combination of the duration and magnitude of ischemia, the nutrients and oxygen content of blood, the specific cerebral structure involved, and ability of the tissue to dissipate the metabolic heat. Cell viability may be lost in as little as 20 minutes after cessation of blood flow. In mild but prolonged low perfusion states, irreversible gray matter damage will occur with CBF below approximately 20 mL/100 mg/h.* Figures 1 to 3 demonstrate a basic concept of

A

B

Figure 1 A) Physiological mechanisms of ion equilibrium in the neuron. The energy of in-flowing sodium ions is utilized for expelling the ions of calcium. Sodium is then removed by the Na⁺/K⁺ pump. The negative potential of the cell interior helps keep the NMDA-coupled calcium channel locked with the ions of magnesium and inhibits the voltage-dependent calcium channels. nNOS – neuronal nitric oxide synthase, NMDA – glutamate (N-methyl-D-spartate) receptor, ATP – adenosinetriphosphate. B) Ischemia and consequent energy deficit cause depolarization of the cell membrane, reversing the action of the sodium-calcium exchanger and allowing influx of sodium and calcium ions into the cell. Depolarization opens the voltage-dependent calcium channels and releases the magnesium-dependent block of the NMDA – coupled calcium channel. The latter is made patent by glutamate, thus leading to increased synthesis of nitric oxide. Excessive concentration of nitric oxide and calcium leads to cell death.

Figure 2 Biochemical mechanism of excitotoxicity. Energy deficit attenuates re-uptake of glutamate in the synaptic cleft. Increased content of this mediator causes overstimulation of the NMDA receptor, excessive synthesis of nitric oxide and influx of calcium into the cell. This leads to inactivation of mitochondrial enzymes, free radical production and activation of phospholipase A₂. The phospholipase releases arachidonic acid which again attenuates re-uptake of glutamate, thus producing the vicious circle of excitotoxicity.

chain reactions in neuron and glia cells under different ischemic conditions, which eventually lead to cell death.

In general, cerebral ischemia results from: 1) global hypoxia due to respiratory or cardiac arrest, 2) hypoperfusion in patients with high ICP, usually in patients after intracranial hemorrhage or head injury, 3) arterial occlusion by embolic material, and 4) subacute or chronic borderline hypoperfusion due to occlusion or

narrowing of large cerebral arteries. The last three need more explanation for the purposes of this review.

Cerebral blood flow disturbances in patients with high ICP

According to the *Monro-Kellie hypothesis* 66, the cranium acts as a near rigid container of virtually incompressible substances such as brain

Figure 3 "Direct" and "indirect" effects of reactive oxygen species (ROS). Reactive oxygen species directly interact with DNA, proteins and lipids and destroy them through oxidation process causing cell death (direct effect). A high ROS concentration damages the structure and function of mitochondria and changes the redox state of the cell interior (indirect effect). Damage to the mitochondria leads to release of factors initiating the process of programmed cell death (apoptosis). Oxidative stress activates transcription factor NFκB (nuclear factor κB), which induce synthesis of many proinflammatory cytokines and adhesion molecules. Increased expression of cytokines and adhesion molecules augments the inflammatory process in neural tissue.

(80%), blood (12%) and cerebrospinal fluid (CSF) (8%). These three volumes completely fill the intracranial cavity and remain in a state of dynamic equilibrium with each other. Based on these premises, any extra volume added to the intracranial cavity will increase ICP. However, cessation of cardiac action leads to equalization of ICP with atmospheric pressure, no matter how high it was before stoppage of cerebral circulation. In other words, it will always equal

zero when the heart does not beat. Thus, it goes without saying that ICP is closely related to the function of cardiovascular system. Under normal CPP (80-100 mmHg), ICP is not higher than 15 mmHg⁶⁷. Blood pressure in the cerebral arteries decreases as the arterial diameter narrows and approaches the interstitial tissue pressure, which is equal to ICP at the level of brain capillaries and veins. High ABP inside the arterial system is not transmitted to

the brain tissue because it is confined within the arteries by thick arterial walls. Moreover, during every cardiac systole, some CSF and venous blood is pushed out of the cranium to accommodate the “cerebral” portion of stroke volume. Thus, under normal conditions, the cranial cavity exhibits some compliance and there is only a slight rise in ICP due to distention of cerebral arteries during cardiac systole.

As mentioned before, any extra space occupied by an intracranial lesion is at the cost of the volume of other intracranial components in order to maintain the ICP at normal levels. Thus, during growth of tumors or the development of hematoma, CSF is absorbed and venous blood is pushed out of the cerebral veins to accommodate the volume of the abnormal lesion inside the skull. When these compensatory mechanisms are exhausted, ICP increases logarithmically as the pathologic volume further increases⁶⁸. As ICP increases, the CPP and consequently CBF begin to decrease. From then on, the highest priority is maintaining CBF, even at the price of a further increase in ICP, as neural tissue is much more sensitive to ischemia than to pressure. It has been shown that neurons can withstand pressure several times higher than atmospheric pressure⁶⁹.

A decrease in CPP lowers intraluminal ABP and leads to dilation of arteries through the vasogenic mechanism. Furthermore, excessive buildup of CO₂, potassium ions, and adenosine add to the effect of hypoxia resulting from insufficient CBF to cause vasodilation. Unfortunately, at this point, even significant vasodilation does not much help in improving CBF. Increased ICP constricts cerebral veins and is transmitted through their thin compliant walls so that the point of maximal resistance of the cerebral vascular bed shifts from arterial to venous system⁷⁰. In other words, CBF decreases because of a lower and lower pressure gradient between the arterial and venous systems. High pressure in the venous system decreases venous outflow and leads to congestive brain swelling.

Under these conditions, general cerebral vasodilation has even more deleterious effects. Dilated arteries contain more blood and increased cerebral blood volume further increases ICP. Moreover, maximal arterial dilation profoundly decreases the stiffness of arterial walls, which become good transmitters of intraluminal ABP into the brain parenchyma⁶⁹. Thus, increased cerebral blood volume, the transmission of intraluminal ABP into brain parenchyma, as well as decreased venous outflow are the main de-

terminants of ICP increase. In this situation, the dynamic system consisting of the intracranial cavity and its contents loses its compliance and becomes “stiff” so that even a small additional volume of systolic blood surge leads to a huge ICP increase⁷¹. When ICP reaches the level of ABP, CPP decreases to zero leading to complete cessation of CBF. It will restart only if ABP rises sufficiently beyond the ICP to restore CBF. If this fails to occur, brain death occurs.

When the hemodynamic disturbances caused by pathologic intracranial volume overcome physiologic mechanisms of intracranial volume compensation, ICP not only increases but also random ICP fluctuations begin to occur more frequently^{72,73}. The increase in CPP may be generated by the Cushing phenomenon, which is activated when brainstem ischemia triggers systemic hypertension, thus increasing CPP⁷⁴. Patients may have severe headache, visual disturbances, impairment of postural or motor control, altered consciousness, bradycardia and high ABP. However, in many patients these symptoms may not occur and brainstem herniation ensues with minimal warning signs.

Based on these facts, two very important conclusions should be drawn, which are relevant for clinical practice. First, there is no perfect relation between clinical signs and severity of intracranial hypertension, and second, monitoring and maintaining CBF is the highest priority to treat patients with intracranial hypertension. Thus, detection of hemodynamic disturbances and close monitoring of CBF are extremely important when taking care of patients with intracranial pathology.

Cerebral emboli and vasospasm in patients after subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) composes half of all spontaneous intracranial hemorrhages; the other half consists of intraparenchymal hematoma, which is a bleeding directly into brain parenchyma.

Rupture of an intracranial aneurysm is the most common cause of SAH. The annual incidence of SAH in the United States 21,000 and 33,000 people⁷⁷. Other causes of SAH include AVM (incidence: 0.55 per 100,000 person-years⁷⁸) drugs (incidence: 0.01 per 100,000 person years⁷⁹), trauma (21.9 to 19.4 per 100,000 population⁸⁰) and primary or secondary neoplasms.

Ruptured cerebral aneurysms present several management challenges. In addition to the high initial mortality and the risk of rebleeding, ap-

proximately 30% of patients develop signs of cerebral ischemia^{81,82}. This can be frustrating, particularly when it follows a successful procedure to secure the ruptured aneurysm. Delayed ischemic deficit (DID) prolongs intensive care unit (ICU) and hospital stays, increases cost and worsens outcome⁸³. Unfortunately, DID remains quite common⁸⁴⁻⁸⁶, and routine neuroimaging studies show an even higher incidence of small, asymptomatic ischemic lesions.

In the 1940s, experimental studies revealed that cerebral vasospasm and cerebral ischemia could be produced by a number of stimuli⁹¹, and it was soon suggested that subarachnoid hemorrhage (SAH) was one of them⁹². The arteriographic demonstration of vasospasm⁹³ and the analysis of several cerebral infarcts in aneurysm patients cemented the relationship between the two⁹⁴⁻⁹⁷. Based on these observations, a series of quite reasonable assumptions was made, on which the understanding of vasospasm pathogenesis still rests. It is assumed that:

- A substance in the subarachnoid blood clot irritates &/or injures exposed cerebral vessels
- They constrict in response
- This produces cerebral ischemia
- Rapid reversal of constriction can restore normal cerebral perfusion.

The association between the constriction of major cerebral arteries and cerebral ischemia has been taken, almost as an article of faith, to be one of cause and effect. Nowadays, despite isolated controversy⁹⁸, the two are commonly distinguished by being termed “angiographic” and either “clinical” or “symptomatic” vasospasm. Research on vasospasm has proceeded along these lines for more than four decades. A recent Medline search revealed more than 40,000 articles devoted to one or another aspects of cerebral vasospasm after SAH.

However, there are a number of theoretical objections, which have been raised against the pairing of “angiographic” and “clinical” vasospasm. Although large cerebral arteries contribute more to vascular resistance than arteries elsewhere in the body, their contribution to regulation of cerebral blood flow (CBF) is relatively minor⁹⁹. Since we cannot visualize the smaller (<100 micron diameter) arteries on arteriography, we must assume they react, as do larger arteries. There is little correlation between the sites and severity of vasospasm and either symptomatic^{92,100} or measured^{101,102} cerebral ischemia. DID symptoms and findings often follow peak vasospasm by several days. The presence and location of angiographic va-

sospasm fails to correlate with areas of cerebral infarction in as many as a third of cases¹⁰³. There are cases in which documented subarachnoid hemorrhage-induced ischemia occurs in the absence of vasospasm¹⁰⁴. It is possible to increase CBF in experimental vasospasm without affecting the spasm itself¹⁰⁵. Minhas et al. performed simultaneous PET and transcranial Doppler (TCD) studies after SAH¹⁰⁶. They failed to find a correlation between the two, thereby “calling into question the traditional concept of large-vessel vasospasm”.

Autopsy studies of SAH reveal that the majority of infarctions involve the cerebral cortex and are widespread and scattered, small, wedge-shaped or laminar¹⁰⁷⁻¹⁰⁹. In one study of 156 patients who died without surgery, 76% had small infarcts, vs. fewer than 6% with large, territorial infarctions¹⁰⁷. These small infarcts were often immediately beneath the thickest subarachnoid clots¹⁰⁷. Neil-Dwyer et al. suggested a diffuse microangiopathy as the major cause of DID¹⁰⁹.

It must also be admitted that aggressive therapy, based on preventing or reversing vasospasm, has had only limited effect on patient outcomes^{85,110-113}. The use of hypertension, hypervolemia, and hemodilution (“triple-H” therapy) after SAH does reduce the incidence of angiographic vasospasm without any significant effect on DID¹¹⁴. Intracisternal implantation of nicardipine pellets prevented angiographic vasospasm but not DID¹¹⁵. Endovascular treatment of aneurysms is associated with less frequent and less severe angiographic vasospasm; however, there was no benefit in overall outcome compared with surgery¹¹². Although transluminal angioplasty is quite effective in reversing angiographic vasospasm, its effect on patient outcome was disappointing^{116,117}.

There is evidence that the small arterioles responsible for CBF control do not react identically to larger, angiographically visible arteries. Surface arteries, even small ones, can be constricted without decreasing CBF^{118,119}. The effects of SAH on the cerebral microcirculation are unclear. A recent review reported contradictory results¹²⁰.

If vasospasm is not responsible for all DID, we must seek alternative possibilities. One such alternative is the possibility that blood or its breakdown products are directly neurotoxic. This is certainly the case. However, animal models of SAH¹²¹⁻¹²⁴ and those which involve exposure to blood products¹²⁵ demonstrate that ischemia invariably precedes necrosis.

Another possible explanation for these multiple microinfarcts arises from thromboembolic phenomena. These stem from two likely mechanisms: endothelial damage and tissue thromboplastin activation. The subarachnoid clot induces mechanical injury and an inflammatory response in the arterial endothelium, which in turn causes local platelet adhesion and thrombosis. A second mechanism involves chemical activation by the clot of tissue thromboplastin (tissue factor, TF). TF is a transmembrane protein residing primarily in the adventitia of the artery. When activated, the TF pathway assembles thrombin complexes on the pericyte membranes to cause intravascular thrombosis¹²⁶. The fate of microthrombi created by either mechanism depends on vessel size. In larger arteries, microclots are likely to embolize. Small arterioles would be more liable to thrombose. Several investigators have demonstrated that microemboli can indeed cause cerebral infarction and symptomatic ischemia^{127,128}.

There is ample evidence supporting an inflammatory response of the arterial endothelium in response to SAH¹²⁹⁻¹³¹. Following SAH, inflammatory genes are upregulated¹³², and inflammatory mediators are released into the blood and CSF^{124,133-141}, as are adhesion molecules¹⁴²⁻¹⁴⁴ and other potential vascular toxins¹⁴⁵⁻¹⁴⁷. Some patients exhibit evidence of acute systemic inflammatory response syndrome (SIRS), an indicator of ischemic complications and poor outcome^{137,148,149}. There is also considerable injury to the vascular endothelium¹⁵⁰⁻¹⁵⁴ with desquamation^{120,152,153}. This is accompanied by the appearance of serum markers of endothelial activation^{155,156}, blood-brain barrier dysfunction^{153,157-159} and platelet accumulation^{154,160}.

In support of the second thrombotic mechanism, the brain has been identified for years as having the body's highest concentrations of TF^{161,162}, much of it localized in the adventitia of cerebral arteries^{163,164} and perivascular astrocytes¹⁶⁵. Recent evidence suggests that TF in the arterial walls plays a major role in thrombosis¹⁶⁶, and that the two prothrombotic mechanisms reinforce each other¹⁶⁷.

As in traumatic brain injury, this is a focal form of disseminated intravascular coagulation^{168,169}. *SAH is rapidly followed by activation of both platelets and coagulation. Markers of hypercoagulation, factor consumption*^{135,170-174} *and platelet activation*^{133,134,140,142,175} *appear soon after the hemorrhage, as do signs of fibrinolysis*^{173,176-178}. When compared with systemic levels, values of these markers are always higher in the CSF

^{171,174,176,177} and jugular venous blood^{135,179} suggesting their cerebral origin. Severe or prolonged elevation is usually associated with more severe DID^{180,181} or worse outcome^{182,183}.

Platelet aggregation¹⁸⁴ and isolated thromboemboli have been noted in the cortical arteries of experimental animals^{154,185,186} and SAH patients at autopsy^{107,187,188}. TCD measurements detected microembolic signals (MES) in many ruptured aneurysms, even in areas not subjected to proximal vasospasm¹⁸⁹⁻¹⁹¹. Romano et al. performed middle cerebral artery TCD monitoring for 30 minutes three times a week during the ICU stay of 23 patients with ruptured aneurysms. MES were detected in 70% of the patients and 32% of the insonated vessels¹⁹¹. *These findings suggest that a huge number of emboli, some of which may be causing symptomatic cerebral infarctions, occur after subarachnoid hemorrhage. Routine CT and MRI studies have documented multiple small infarcts*^{89,182,190} *the incidence in most series being between 44% and 67%.* There was a strong association between the number of MES and the presence of DID in most series. Rordorf et al. studied six patients with combined diffusion and perfusion MRIs¹⁹². They confirmed widespread ischemic lesions, surrounded by areas of reduced CBF. In addition, Peltonen et al. found a positive correlation between coagulopathy and later appearance of infarcts¹⁸².

*The occurrence of thromboembolism after SAH allows reinterpretation of several observations, which would be difficult to explain otherwise. Although microclots are also quite common after traumatic brain injury, they are rarely noted on histologic examination unless special stains are used*¹⁹³. This may account for the infrequent mention of such clots after SAH. It is worth noting that arterial occlusions are illustrated without more than cursory acknowledgement in the two large autopsy series referred to above^{108,109}.

A number of treatments reported to have some success in preventing or combatting DID also have anticoagulant effects. Protease inhibitors, which have been shown to prevent vasospasm, also inhibit clotting factors^{138,194,195}. Aspirin and other NSAIDs are known to protect against vascular spasm and DID¹⁹⁶⁻¹⁹⁸. Nimodipine, which is effective against DID, does not prevent vasospasm^{199,200}. Perhaps its fibrinolytic²⁰¹ or anti-platelet²⁰² properties account for its success. Statins protect against DID^{203,204} and have also been found to reduce microclot formation after brain injury^{205,206}.

A number of effective anti-inflammatory agents also have antiplatelet and anticoagulant properties²⁰⁷⁻²⁰⁹. It must be remembered that coagulation is an integral part of the inflammatory reaction; the two processes are mutually reinforcing²¹⁰⁻²¹². Hemodilution treatment, to the extent that it prevents DID, also inhibits blood coagulation. Early lysis of subarachnoid clots with intracisternal tissue plasminogen activator shows great promise in preventing vasospasm and DID²¹³. Of course, this also prevents thromboembolic activity. Interestingly, one study of intrathecal urokinase had a more striking effect on DID than on vasospasm, suggesting the two might have different mechanisms²¹⁴. The association of antifibrinolytic therapy, popular in the 1970s, with vasospasm and DID is well-documented²¹⁵. *Finally, a number of recent reports have noted a high incidence (20-60%) of small infarcts revealed by MRI scans taken after coil occlusion of ruptured cerebral aneurysms*^{189,216-218}. Most of these authors implied that this was a complication of endovascular therapy, although the infarct could have just as easily arisen from spontaneous thromboemboli. Supporting the latter hypothesis is the finding that follow-up imaging frequently reveals new lesions proximal to the treated aneurysms²¹⁹.

Patients after SAH are therefore not only at high risk of developing cerebral infarcts arising from spontaneous thromboemboli, but also at high risk of developing overlapping ischemia due to cerebral vasospasm^{220,221} *and rising ICP, which can further alter the cerebral hemodynamics.* It is estimated that 67% of patients with SAH develop cerebral vasospasm sometime after the ictus, however, the time when it occurs cannot be predicted accurately based on clinical signs. Vasospasm can begin as early as three to four hours after SAH, and typically in acute phase involves small vessels, whereas three to five days later it usually affects larger vessels with a maximal narrowing occurring approximately between days six and eight²²⁰. Vasospasm can resolve without treatment two to three weeks after SAH²²². *Detection and monitoring of cerebral vasospasm and hemodynamic disturbances are absolutely critical for prompt administration of aggressive preventive stroke therapy.*

Treatment of vasospasm in patients with SAH

The stroke preventive strategy after aneurysm rupture includes urgent craniotomy and clipping, or intravascular coiling (as early as

feasible) of the aneurysm to prevent re-bleeding and to permit further aggressive management to address abnormalities of brain oxygenation, glucose metabolism, and hemodynamic instability that can potentially exacerbate diffuse hypoxic/ischemic injury after the initial hemorrhage. Interventions targeted at normalization of these derangements, such as tight blood-pressure control, brain tissue oxygen-tension-directed therapy, or continuous insulin infusion, are reasonable therapeutic options given the current state of knowledge.

In SAH patients who survive the first days after bleeding, vasospasm and cerebral ischemia are important contributors to poor outcome²²³. Cerebral autoregulation is often disturbed in SAH patients²²⁴. In the presence of vasospasm or microthrombosis this may result in decreased CBF and thereby stroke^{224,225}. When autoregulation is affected, CBF becomes dependent on cerebral perfusion pressure and blood viscosity. To increase CBF different combinations of hemodilution, hypervolemia, and hypertension have been used²²⁶. When all three components are used, the treatment combination is called triple-H²²⁷. *However, triple-H and its components are associated with increased complications*^{227,228}, *such as increased cerebral edema or hemorrhagic transformation in areas of infarction, congestive heart failure, or pulmonary edema.* A recent systematic review of the controlled studies on the effect of triple-H components on cerebral perfusion in SAH patients showed no clear benefits of triple-H therapy²²⁹. However, owing to the number of underpowered and poorly designed studies, it is difficult to come to any conclusions regarding the effectiveness of triple-H therapy. *Thus, triple-H therapy is suggested to be used when the diagnosis of vasospasm is made rather than prophylactically*^{230,231}. Accumulating literature has shifted the focus from this triple-H therapy to the maintenance of euvolemia and induced hypertension²²⁹.

A Cochrane review, including 16 trials with 3,361 SAH patients, found a relative risk of 0.81 (95% CI, 0.72–0.92) for death or dependence in the patients treated with calcium antagonists; the corresponding number of patients needed to treat was 19 (95% CI, 1–51)²³². For oral nimodipine alone the RR was 0.67 (95% CI, 0.55–0.81); for other calcium antagonists or intravenous administration of nimodipine the results were not statistically significant. Calcium antagonists reduced the occurrence of secondary ischemia and showed a favorable trend for case

fatality. Nimodipine has been shown, in four randomized, double-blind, placebo-controlled trials, to reduce the severity of neurological deficits resulting from vasospasm in patients who have had a recent SAH²³³. Three of the trials studied relatively well patients, with all or most patients in Hunt and Hess Grades I to III (essentially free of focal deficits after the initial bleed), while the fourth studied much sicker patients, Hunt and Hess Grades III to V. In each trial, a judgment was made as to whether any late-developing deficit was due to spasm or other causes, and the deficits were graded. No effect was seen on deficits not related to spasm. Although it is not confirmed that nimodipine prevents vasospasm, the practical implication is that the regimen in the dominant nimodipine trial (60 mg orally every 4 h for three weeks) is currently regarded as the standard treatment in patients with aneurysmal SAH^{233,234}. Contrary to the promising positive results of small single-center studies, recently published results from placebo-controlled randomized trials and meta-analyses did not show any effect of statins or magnesium on the development or clinical outcome of cerebral vasospasm after SAH²³⁵⁻²³⁷.

When medical treatment is unsuccessful, endovascular methods (e.g., intra-arterial infusion of vasodilative agents, or balloon angioplasty) may restore flow. The outcome of patients who develop vasospasm, and in particular delayed cerebral ischemia (DCI) associated with vasospasm, is improved with early treatment. However, when to initiate various interventions often may be uncertain because the diagnosis and monitoring of vasospasm may be difficult and unreliable when based solely on the neurologic examination. Furthermore, other complications common in SAH patients, such as recurrent hemorrhage, hydrocephalus, metabolic disorders, and seizures, can produce similar neurologic symptoms²³⁰.

Detection of vasospasm in patients after SAH based on clinical evaluation

The clinical diagnosis of vasospasm in SAH patients can be difficult, and in many cases not possible at all because a variety of non-specific clinical symptoms, such as focal neurologic deficits or more global deficits related to decreased level of consciousness, confusion, or agitation

that can be caused by cerebral edema, seizure, fever, metabolic disturbance, and drug reaction. Most importantly, many SAH patients are in poor neurological condition at presentation or receiving sedative medication, making identification of new neurological deficits due to vasospasm challenging.

The most objective indicator of the poor utility of clinical evaluation for the detection of vasospasm is perhaps the reported incidence of delayed asymptomatic cerebral infarction in patients with SAH. Rabinstein et al.²³⁸ retrospectively evaluated 143 SAH patients in whom CT scans were obtained as clinically indicated, with delayed asymptomatic cerebral infarction developing in 11% of SAH patients. Prospectively obtained data from 580 SAH patients in the Subarachnoid Hemorrhage Outcomes Project revealed delayed asymptomatic cerebral infarction in 4% of SAH patients, which represented 20% of all DCI cases²³⁹. In this large cohort, infarcts were more common in comatose patients and were associated with a worse patient outcome in long-term follow-up (despite their categorization as “asymptomatic”), Shimoda et al.²⁴⁰ prospectively evaluated 125 SAH patients with serial MRI studies obtained at predetermined time points, i.e., immediately following surgical or endovascular aneurysm treatment and on post-SAH days 3, 14, and 30. They found that 23% of SAH patients developed a delayed asymptomatic cerebral infarction. These data support a need for aggressive monitoring of patients with SAH who are in poor neurological condition and cannot be accurately assessed clinically.

There are many current diagnostic imaging modalities in place such as digital subtraction angiography, computed tomographic angiography (CTA), magnetic resonance angiography, transcranial doppler ultrasonography and transcranial color-coded doppler ultrasonography. New guidelines for the diagnosis and management of subarachnoid hemorrhage (SAH) based on levels of evidence, updating the guidelines last published in 1994, have recently been published by Connolly et al.^{234,241}. It should be noted that many of the methods used to monitor aneurysm rupture and the ensuing cerebral vasospasm are a current topic of constant debate. An overview of diagnostic and monitoring methods will be provided in the next issue of The Neuroradiology Journal.

References

- 1 Ito H, Kanno I, Kato C, et al. Database of normal human cerebral blood flow, cerebral blood volume, cerebral oxygen extraction fraction and cerebral metabolic rate of oxygen measured by positron emission tomography with 15O-labelled carbon dioxide or water, carbon monoxide and oxygen: a multicentre study in Japan. *Eur J Nucl Med Mol Imaging*. 2004; 31: 635-643.
- 2 Helenius J, Perkio J, Soinne L, et al. Cerebral hemodynamics in a healthy population measured by dynamic susceptibility contrast MR imaging. *Acta Radiol*. 2003; 44: 538-546.
- 3 Chih CP, Roberts Jr EL. Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis. *J Cereb Blood Flow Metab*. 2003; 23: 1263-1281.
- 4 Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. *Semin Thromb Hemost*. 2003; 29: 435-450.
- 5 McDonald DA. Arterial impedance. In: McDonald DA ed. *Blood flow in arteries*. Baltimore: Williams&Wilkins Co; 1977. p. 351-389.
- 6 McDonald DA. The numerical analysis of circulatory wave-forms. In: McDonald DA ed. *Blood flow in arteries*. Baltimore: Williams&Wilkins Co; 1974. p.146-173.
- 7 Lassen NA. Cerebral blood flow and oxygen consumption in man. *J Physiol Rev*. 1959; 39: 183-238.
- 8 Strandgaard S, Olesen J, Skinhoj E, et al. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J*. 1973; 1: 507-510.
- 9 Waldemar G, Schmidt JF, Andersen AR, et al. Angiotensin converting enzyme inhibition and cerebral blood flow autoregulation in normotensive and hypertensive man. *J Hypertens*. 1989; 7: 229-235.
- 10 Wallis SJ, Firth J, Dunn WR. Pressure-induced myogenic responses in human isolated cerebral resistance arteries. *Stroke*. 1996; 27: 2287-2290; discussion 2291.
- 11 Garcia-Roldan JL, Bevan JA. Flow-induced constriction and dilation of cerebral resistance arteries. *Circ Res*. 1990; 66: 1445-1448.
- 12 Thorin-Trescases N, Bevan JA. High levels of myogenic tone antagonize the dilator response to flow of small rabbit cerebral arteries. *Stroke*. 1998; 29: 1194-1200; discussion 1200-1191.
- 13 McDonald DA. *Blood flow in arteries*. Baltimore: Williams & Wilkins Co; 1977.
- 14 Shish DF, Welsh DG, Brayden JE. Diacylglycerol and protein kinase C activate cation channels involved in myogenic tone. *Am J Physiol Heart Circ Physiol*. 2002; 283: H2196-2201.
- 15 Kitamura K, Xiong Z, Teramoto N, et al. Roles of inositol trisphosphate and protein kinase C in the spontaneous outward current modulated by calcium release in rabbit portal vein. *Pflugers Arch*. 1992; 421: 539-551.
- 16 McCarron JG, Crichton CA, Langton PD, et al. Myogenic contraction by modulation of voltage-dependent calcium currents in isolated rat cerebral arteries. *J Physiol*. 1997; 498 (Pt 2): 371-379.
- 17 Ngai AC, Winn HR. Modulation of cerebral arteriolar diameter by intraluminal flow and pressure. *Circ Res*. 1995; 77: 832-840.
- 18 Faraci FM. Role of nitric oxide in regulation of basilar artery tone *in vivo*. *Am J Physiol*. 1990; 259: H1216-1221.
- 19 Lee JE, Kwak J, Suh CK, et al. Dual effects of nitric oxide on the large conductance calcium-activated potassium channels of rat brain. *J Biochem Mol Biol*. 2006; 39: 91-96.
- 20 Miyahara K, Kawamoto T, Sase K, et al. Cloning and structural characterization of the human endothelial nitric-oxide-synthase gene. *Eur J Biochem*. 1994; 223: 719-726.
- 21 Kontos HA, Raper AJ, Patterson JL. Analysis of vasoactivity of local pH, PCO₂ and bicarbonate on pial vessels. *Stroke*. 1977; 8: 358-360.
- 22 Horiuchi T, Dietrich HH, Hongo K, et al. Role of endothelial nitric oxide and smooth muscle potassium channels in cerebral arteriolar dilation in response to acidosis. *Stroke*. 2002; 33: 844-849.
- 23 Kovacs K, Komjati K, Marton T, et al. Hypercapnia stimulates prostaglandin E(2) but not prostaglandin I(2) release in endothelial cells cultured from microvessels of human fetal brain. *Brain Res Bull*. 2001; 54: 387-390.
- 24 Lindauer U, Vogt J, Schuh-Hofer S, et al. Cerebrovascular vasodilation to extraluminal acidosis occurs via combined activation of ATP-sensitive and Ca²⁺-activated potassium channels. *J Cereb Blood Flow Metab*. 2003; 23: 1227-1238.
- 25 Toda N, Hatano Y, Mori K. Mechanisms underlying response to hypercapnia and bicarbonate of isolated dog cerebral arteries. *Am J Physiol*. 1989; 257: H141-146.
- 26 Simpson RE, Phillis JW. Adenosine deaminase reduces hypoxic and hypercapnic dilatation of rat pial arterioles: evidence for mediation by adenosine. *Brain Res*. 1991; 553: 305-308.
- 27 Fredricks KT, Liu Y, Rusch NJ, et al. Role of endothelium and arterial K⁺ channels in mediating hypoxic dilation of middle cerebral arteries. *Am J Physiol*. 1994; 267: H580-586.
- 28 Horiuchi T, Dietrich HH, Hongo K, et al. Mechanism of extracellular K⁺-induced local and conducted responses in cerebral penetrating arterioles. *Stroke*. 2002; 33: 2692-2699.
- 29 Di Tullio MA, Tayebati SK, Amenta F. Identification of adenosine A1 and A3 receptor subtypes in rat pial and intracerebral arteries. *Neurosci Lett*. 2004; 366: 48-52.
- 30 Kleppisch T, Nelson MT. Adenosine activates ATP-sensitive potassium channels in arterial myocytes via A2 receptors and cAMP-dependent protein kinase. *Proc Natl Acad Sci USA*. 1995; 92: 12441-12445.
- 31 Li G, Cheung DW. Modulation of Ca(2+)-dependent K(+) currents in mesenteric arterial smooth muscle cells by adenosine. *Eur J Pharmacol*. 2000; 394: 35-40.
- 32 Bleys RL, Cowen T. Innervation of cerebral blood vessels: morphology, plasticity, age-related, and Alzheimer's disease-related neurodegeneration. *Microsc Res Tech*. 2001; 53: 106-118.
- 33 Baffi J, Gorcs T, Slowik F, et al. Neuropeptides in the human superior cervical ganglion. *Brain Res*. 1992; 570: 272-278.
- 34 Baumbach GL, Heistad DD. Effects of sympathetic stimulation and changes in arterial pressure on segmental resistance of cerebral vessels in rabbits and cats. *Circ Res*. 1983; 52: 527-533.
- 35 Goadsby PJ, Uddman R, Edvinsson L. Cerebral vasodilatation in the cat involves nitric oxide from parasympathetic nerves. *Brain Res*. 1996; 707: 110-118.
- 36 Hara H, Hamill GS, Jacobowitz DM. Origin of cholinergic nerves to the rat major cerebral arteries: coexistence with vasoactive intestinal polypeptide. *Brain Res Bull*. 1985; 14: 179-188.
- 37 Morita-Tsuzuki Y, Hardebo JE, Bouskela E. Inhibition of nitric oxide synthase attenuates the cerebral blood flow response to stimulation of postganglionic parasympathetic nerves in the rat. *J Cereb Blood Flow Metab*. 1993; 13: 993-997.
- 38 Edvinsson L, Ekman R, Jansen I, et al. Calcitonin gene-related peptide and cerebral blood vessels: distribution and vasomotor effects. *J Cereb Blood Flow Metab*. 1987; 7: 720-728.
- 39 Edvinsson L, Brodin E, Jansen I, et al. Neurokinin A in cerebral vessels: characterization, localization and effects *in vitro*. *Regul Pept*. 1988; 20: 181-197.
- 40 Edvinsson L, Jansen Olesen I, Kingman TA, et al. Modification of vasoconstrictor responses in cerebral

- blood vessels by lesioning of the trigeminal nerve: possible involvement of CGRP. *Cephalalgia*. 1995; 15: 373-383.
- 41 Lassen LH, Haderslev PA, Jacobsen VB, et al. CGRP may play a causative role in migraine. *Cephalalgia*. 2002; 22: 54-61.
 - 42 Weber JR, Angstwurm K, Bove GM, et al. The trigeminal nerve and augmentation of regional cerebral blood flow during experimental bacterial meningitis. *J Cereb Blood Flow Metab*. 1996; 16: 1319-1324.
 - 43 Kalaria RN, Stockmeier CA, Harik SI. Brain microvessels are innervated by locus ceruleus noradrenergic neurons. *Neurosci Lett*. 1989; 97: 203-208.
 - 44 Moreno MJ, Lopez de Pablo A, Conde MV, et al. Cat cerebral arteries are functionally innervated by serotonergic fibers from central and peripheral origins. *Stroke*. 1995; 26: 271-275; discussion 275-276.
 - 45 Sato A, Sato Y, Uchida S. Activation of the intracerebral cholinergic nerve fibers originating in the basal forebrain increases regional cerebral blood flow in the rat's cortex and hippocampus. *Neurosci Lett*. 2004; 361: 90-93.
 - 46 Cauli B, Tong XK, Rancillac A, et al. Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. *J Neurosci*. 2004; 24: 8940-8949.
 - 47 Mulligan SJ and MacVicar BA. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. *Nature*. 2004; 431: 195-199.
 - 48 White RP, Hindley C, Bloomfield PM, et al. The effect of the nitric oxide synthase inhibitor L-NAME on basal CBF and vasoneuronal coupling in man: a PET study. *J Cereb Blood Flow Metab*. 1999; 19: 673-678.
 - 49 Belliveau JW, Kennedy DN, Jr., McKinstry RC, et al. Functional mapping of the human visual cortex by magnetic resonance imaging. *Science*. 1991; 254: 716-719.
 - 50 Zonta M, Angulo MC, Gobbo S, et al. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat Neurosci*. 2003; 6: 43-50.
 - 51 Bezzi P, Carmignoto G, Pasti L, et al. Prostaglandins stimulate calcium-dependent glutamate release in astrocytes. *Nature*. 1998; 391: 281-285.
 - 52 Bhardwaj A, Northington FJ, Carhuapoma JR, et al. P-450 epoxygenase and NO synthase inhibitors reduce cerebral blood flow response to N-methyl-D-aspartate. *Am J Physiol Heart Circ Physiol*. 2000; 279: H1616-1624.
 - 53 Gebremedhin D, Lange AR, Lowry TF, et al. Production of 20-HETE and its role in autoregulation of cerebral blood flow. *Circ Res*. 2000; 87: 60-65.
 - 54 Christopherson KS, Hillier BJ, Lim WA, et al. PSD-95 assembles a ternary complex with the N-methyl-D-aspartic acid receptor and a bivalent neuronal NO synthase PDZ domain. *J Biol Chem*. 1999; 274: 27467-27473.
 - 55 Pelligrino DA, Gay RL, 3rd, Baughman VL, et al. NO synthase inhibition modulates NMDA-induced changes in cerebral blood flow and EEG activity. *Am J Physiol*. 1996; 271: H990-995.
 - 56 Alonso-Galicia M, Drummond HA, Reddy KK, et al. Inhibition of 20-HETE production contributes to the vascular responses to nitric oxide. *Hypertension*. 1997; 29: 320-325.
 - 57 Sun CW, Falck JR, Okamoto H, et al. Role of cGMP versus 20-HETE in the vasodilator response to nitric oxide in rat cerebral arteries. *Am J Physiol Heart Circ Physiol*. 2000; 279: H339-350.
 - 58 Kara T, Narkiewicz K, Somers VK. Chemoreflexes-physiology and clinical implications. *Acta Physiol Scand*. 2003; 177: 377-384.
 - 59 Heistad DD, Marcus ML, Ehrhardt JC, et al. Effect of stimulation of carotid chemoreceptors on total and regional cerebral blood flow. *Circ Res*. 1976; 38: 20-25.
 - 60 Mitchell RA. Respiratory chemosensitivity in the medulla oblongata. *J Physiol*. 1969; 202: 3P-4P.
 - 61 Jordan J, Shannon JR, Diedrich A, et al. Interaction of carbon dioxide and sympathetic nervous system activity in the regulation of cerebral perfusion in humans. *Hypertension*. 2000; 36: 383-388.
 - 62 Roatta S, Miceli G, Bosone D, et al. Effect of generalised sympathetic activation by cold pressor test on cerebral haemodynamics in healthy humans. *J Auton Nerv Syst*. 1998; 71: 159-166.
 - 63 Heistad DD, Marcus ML. Total and regional cerebral blood flow during stimulation of carotid baroreceptors. *Stroke*. 1976; 7: 239-243.
 - 64 Rapela CE, Green HD, Denison AB, Jr. Baroreceptor reflexes and autoregulation of cerebral blood flow in the dog. *Circ Res*. 1967; 21: 559-568.
 - 65 Bondar RL, Kassam MS, Stein F, et al. Simultaneous cerebrovascular and cardiovascular responses during presyncope. *Stroke*. 1995; 26: 1794-1800.
 - 66 Mokri B. The Monroe-Kellie hypothesis: applications in CSF volume depletion. *Neurology*. 2001; 56: 1746-1748.
 - 67 Miller JD. Intracranial pressure monitoring. *Arch Neurol*. 1985; 42: 1191-1193.
 - 68 Kingman TA, Mendelow AD, Graham DI, et al. Experimental intracerebral mass: time-related effects on local cerebral blood flow. *J Neurosurg*. 1987; 67: 732-738.
 - 69 Sahay KB, Mehrotra R, Sachdeva U, et al. Elastomechanical characterization of brain tissues. *J Biomech*. 1992; 25: 319-326.
 - 70 Johnston IH, Rowan JO. Raised intracranial pressure and cerebral blood flow. 3. Venous outflow tract pressures and vascular resistances in experimental intracranial hypertension. *J Neurol Neurosurg Psychiatry*. 1974; 37: 392-402.
 - 71 Ikeyama A, Maeda S, Ito A, et al. The analysis of the intracranial pressure by the concept of the driving pressure from the vascular system. *Neurochirurgia (Stuttg)*. 1978; 21: 43-53.
 - 72 Swiercz M, Mariak Z, Krejza J, et al. Intracranial pressure processing with artificial neural networks: prediction of ICP trends. *Acta Neurochir (Wien)*. 2000; 142: 401-406.
 - 73 Mariak Z, Swiercz M, Krejza J, et al. Intracranial pressure processing with artificial neural networks: classification of signal properties. *Acta Neurochir (Wien)*. 2000; 142: 407-411; discussion 411-402.
 - 74 Ungersbock K, Tenckhoff D, Heimann A, et al. Transcranial Doppler and cortical microcirculation at increased intracranial pressure and during the Cushing response: an experimental study on rabbits. *Neurosurgery*. 1995; 36: 147-156; discussion 156-147.
 - 75 Linn FH, Rinkel GJ, Algra A, et al. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. *Stroke*. 1996; 27: 625-629.
 - 76 Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004; 363: 1925-1933.
 - 77 Zacharia BE, Hickman ZL, Grobelny BT, et al. Epidemiology of aneurysmal subarachnoid hemorrhage. *Neurosurg Clin N Am*. 2010; 21: 221-233.
 - 78 Stapf C, Labovitz DL, Sciacca RR, et al. Incidence of adult brain arteriovenous malformation hemorrhage in a prospective population-based stroke survey. *Cerebrovasc Dis*. 2002; 13: 43-46.
 - 79 Martin-Schild S, Albright KC, Hallevi H, et al. Intracerebral hemorrhage in cocaine users. *Stroke*. 2010; 41: 680-684.
 - 80 Faul M, Xu L, Wald MM, et al. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths, 2002-2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
 - 81 Haley EC, Jr, Kassell NF, Torner JC. The Interna-

- tional cooperative study on the timing of aneurysm surgery. The North American experience. *Stroke*. 1992; 23: 205-214.
- 82 Haley EC, Jr, Kassell NF, Apperson-Hansen C, et al. A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. *J Neurosurg*. 1997; 86: 467-474.
 - 83 Claassen J, Bernardini GL, Kreiter K, et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. *Stroke*. 2001; 32: 2012-2020.
 - 84 Harrod CG, Bendok BR, Batjer HH. Prediction of cerebral vasospasm in patients presenting with aneurysmal subarachnoid hemorrhage: a review. *Neurosurgery*. 2005; 56: 633-654; discussion 633-654.
 - 85 Longstreth WT, Jr, Nelson LM, Koepsell TD, et al. Clinical course of spontaneous subarachnoid hemorrhage: a population-based study in King County, Washington. *Neurology*. 1993; 43: 712-718.
 - 86 Solenski NJ, Haley EC, Jr, Kassell NF, et al. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. *Crit Care Med*. 1995; 23: 1007-1017.
 - 87 Hirashima Y, Kurimoto M, Takaba M, et al. The use of computed tomography in the prediction of delayed cerebral infarction following acute aneurysm surgery for subarachnoid haemorrhage. *Acta Neurochir (Wien)*. 1995; 132: 9-13.
 - 88 Kivisaari RP, Salonen O, Servo A, et al. MR imaging after aneurysmal subarachnoid hemorrhage and surgery: a long-term follow-up study. *Am J Neuroradiol*. 2001; 22: 1143-1148.
 - 89 Dreier JP, Sakowitz OW, Harder A, et al. Focal laminar cortical MR signal abnormalities after subarachnoid hemorrhage. *Ann Neurol*. 2002; 52: 825-829.
 - 90 Juvela S, Siironen J, Varis J, et al. Risk factors for ischemic lesions following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2005; 102: 194-201.
 - 91 Echlin FA. Vasospasm and focal cerebral ischemia: An experimental study. *Arch Neurol Psychiatry*. 1942; 47: 77-96.
 - 92 Robertson EG. Cerebral lesions due to intracranial aneurysms. *Brain*. 1949; 72: 150-185.
 - 93 Ecker A, Riemschneider PA. Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms. *J Neurosurg*. 1951; 8: 660-667.
 - 94 Falconer MA. Surgical pathology of spontaneous intracranial haemorrhage due to aneurysms and arteriovenous malformations. *Proc R Soc Med*. 1954; 47: 693-700.
 - 95 Birse SH, Tom MI. Incidence of cerebral infarction associated with ruptured intracranial aneurysms. A study of 8 unoperated cases of anterior cerebral aneurysm. *Neurology*. 1960; 10: 101-106.
 - 96 Crompton MR. The Pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysms. *Brain*. 1964; 87: 491-510.
 - 97 Schneck SA. On the relationship between ruptured intracranial aneurysm and cerebral infarction. *Neurology*. 1964; 14: 691-702.
 - 98 Mendelow AD. Pathophysiology of delayed ischaemic dysfunction after subarachnoid haemorrhage: experimental and clinical data. *Acta Neurochir Suppl (Wien)*. 1988; 45: 7-10.
 - 99 Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res*. 1990; 66: 8-17.
 - 100 Adams HP, Jr. Prevention of brain ischemia after aneurysmal subarachnoid hemorrhage. *Neurol Clin*. 1992; 10: 251-268.
 - 101 Geraud G, Tremoulet M, Guell A, et al. The prognostic value of noninvasive CBF measurement in subarachnoid hemorrhage. *Stroke*. 1984; 15: 301-305.
 - 102 Ohkuma H, Manabe H, Tanaka M, et al. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2000; 31: 1621-1627.
 - 103 Rabinstein AA, Friedman JA, Weigand SD, et al. Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke*. 2004; 35: 1862-1866.
 - 104 Mathew NT, Meyer JS. Pathogenesis and natural history of transient global amnesia. *Stroke*. 1974; 5: 303-311.
 - 105 Pluta RM, Afshar JK, Thompson BG, et al. Increased cerebral blood flow but no reversal or prevention of vasospasm in response to L-arginine infusion after subarachnoid hemorrhage. *J Neurosurg*. 2000; 92: 121-126.
 - 106 Minhas PS, Menon DK, Smielewski P, et al. Positron emission tomographic cerebral perfusion disturbances and transcranial Doppler findings among patients with neurological deterioration after subarachnoid hemorrhage. *Neurosurgery*. 2003; 52: 1017-1022; discussion 1022-1014.
 - 107 Stoltenberg-Didinger G, Schwarz K. Brain lesions secondary to subarachnoid hemorrhage due to ruptured aneurysms. In: Cervos-Navarro J and Ferszt R ed. *Stroke and Microcirculation*. New York: Raven Press; 1987. p. 471-480.
 - 108 Stoltenberg-Didinger G. Neuropathology of subarachnoid hemorrhage. In: Bederson JB ed. *Subarachnoid hemorrhage: pathophysiology and management*. Park Ridge, IL: American Association of Neurological Surgeons; 1997. p. 41-60.
 - 109 Neil-Dwyer G, Lang DA, Doshi B, et al. Delayed cerebral ischaemia: the pathological substrate. *Acta Neurochir (Wien)*. 1994; 131: 137-145.
 - 110 Ljunggren B, Saveland H, Brandt L. Causes of unfavorable outcome after early aneurysm operation. *Neurosurgery*. 1983; 13: 629-633.
 - 111 Kassell NF, Torner JC, Haley EC, Jr, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. *J Neurosurg*. 1990; 73: 18-36.
 - 112 Rabinstein AA, Pichelmann MA, Friedman JA, et al. Symptomatic vasospasm and outcomes following aneurysmal subarachnoid hemorrhage: a comparison between surgical repair and endovascular coil occlusion. *J Neurosurg*. 2003; 98: 319-325.
 - 113 Hoh BL, Curry WT, Jr, Carter BS, et al. Computed tomographic demonstrated infarcts after surgical and endovascular treatment of aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 2004; 146: 1177-1183.
 - 114 Treggiari MM, Walder B, Suter PM, et al. Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage. *J Neurosurg*. 2003; 98: 978-984.
 - 115 Kasuya H, Onda H, Takeshita M, et al. Efficacy and safety of nicardipine prolonged-release implants for preventing vasospasm in humans. *Stroke*. 2002; 33: 1011-1015.
 - 116 Zubkov AY, Lewis AI, Scalzo D. Transluminal angioplasty and intra-arterial papaverine for the treatment of cerebral vasospasm after ruptured arteriovenous malformations. *Surg Neurol*. 1999; 51: 75-79; discussion 80.
 - 117 Polin RS, Coenen VA, Hansen CA, et al. Efficacy of transluminal angioplasty for the management of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2000; 92: 284-290.
 - 118 Stein SC, Cracco RQ. Cortical injury without ischemia produced by topical monoamines. *Stroke*. 1982; 13: 74-83.
 - 119 Tasdemiroglu E, Macfarlane R, Wei EP, et al. Pial vessel caliber and cerebral blood flow become dis-

- sociated during ischemia-reperfusion in cats. *Am J Physiol.* 1992; 263: H533-536.
- 120 Perkins E, Kimura H, Parent AD, et al. Evaluation of the microvasculature and cerebral ischemia after experimental subarachnoid hemorrhage in dogs. *J Neurosurg.* 2002; 97: 896-904.
 - 121 Dietrich HH, Dacey RG, Jr. Molecular keys to the problems of cerebral vasospasm. *Neurosurgery.* 2000; 46: 517-530.
 - 122 Alkan T, Korfali E, Kahveci N. Experimental subarachnoid haemorrhage models in rats. *Acta Neurochir Suppl.* 2002; 83: 61-69.
 - 123 Prunell GF, Mathiesen T, Diemer NH, et al. Experimental subarachnoid hemorrhage: subarachnoid blood volume, mortality rate, neuronal death, cerebral blood flow, and perfusion pressure in three different rat models. *Neurosurgery.* 2003; 52: 165-175; discussion 175-166.
 - 124 Prunell GF, Svendgaard NA, Alkass K, et al. Inflammation in the brain after experimental subarachnoid hemorrhage. *Neurosurgery.* 2005; 56: 1082-1092; discussion 1082-1092.
 - 125 Dreier JP, Ebert N, Priller J, et al. Products of hemolysis in the subarachnoid space inducing spreading ischemia in the cortex and focal necrosis in rats: a model for delayed ischemic neurological deficits after subarachnoid hemorrhage? *J Neurosurg.* 2000; 93: 658-666.
 - 126 Bouchard BA, Shatos MA, Tracy PB. Human brain pericytes differentially regulate expression of procoagulant enzyme complexes comprising the extrinsic pathway of blood coagulation. *Arterioscler Thromb Vasc Biol.* 1997; 17: 1-9.
 - 127 Rapp JH, Pan XM, Yu B, et al. Cerebral ischemia and infarction from atheroemboli <100 microm in size. *Stroke.* 2003; 34: 1976-1980.
 - 128 Atochin DN, Murciano JC, Gursoy-Ozdemir Y, et al. Mouse model of microembolic stroke and reperfusion. *Stroke.* 2004; 35: 2177-2182.
 - 129 Hoshi T, Shimizu T, Kito K, et al. [Immunological study of late cerebral vasospasm in subarachnoid hemorrhage. Detection of immunoglobulins, C3, and fibrinogen in cerebral arterial walls by immunofluorescence method]. *Neurol Med Chir (Tokyo).* 1984; 24: 647-654.
 - 130 Peterson JW, Kwun BD, Hackett JD, et al. The role of inflammation in experimental cerebral vasospasm. *J Neurosurg.* 1990; 72: 767-774.
 - 131 Dumont AS, Dumont RJ, Chow MM, et al. Cerebral vasospasm after subarachnoid hemorrhage: putative role of inflammation. *Neurosurgery.* 2003; 53: 123-133; discussion 133-125.
 - 132 Aihara Y, Kasuya H, Onda H, et al. Quantitative analysis of gene expressions related to inflammation in canine spastic artery after subarachnoid hemorrhage. *Stroke.* 2001; 32: 212-217.
 - 133 Vinge E, Brandt L, Ljunggren B, et al. Thromboxane B2 levels in serum during continuous administration of nimodipine to patients with aneurysmal subarachnoid hemorrhage. *Stroke.* 1988; 19: 644-647.
 - 134 Juvela S, Kaste M, Hillbom M. Platelet thromboxane release after subarachnoid hemorrhage and surgery. *Stroke.* 1990; 21: 566-571.
 - 135 Hirashima Y, Nakamura S, Endo S, et al. Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. *Neurochem Res.* 1997; 22: 1249-1255.
 - 136 Osuka K, Suzuki Y, Tanazawa T, et al. Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. *Acta Neurochir (Wien).* 1998; 140: 943-951.
 - 137 Gruber A, Rossler K, Graninger W, et al. Ventricular cerebrospinal fluid and serum concentrations of sTNF-R-I, IL-1ra, and IL-6 after aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol.* 2000; 12: 297-306.
 - 138 Zhang Z, Nagata I, Kikuchi H, et al. Broad-spectrum and selective serine protease inhibitors prevent expression of platelet-derived growth factor-BB and cerebral vasospasm after subarachnoid hemorrhage: vasospasm caused by cisternal injection of recombinant platelet-derived growth factor-BB. *Stroke.* 2001; 32: 1665-1672.
 - 139 Kim DE, Suh YS, Lee MS, et al. Vascular NAD(P)H oxidase triggers delayed cerebral vasospasm after subarachnoid hemorrhage in rats. *Stroke.* 2002; 33: 2687-2691.
 - 140 Borel CO, McKee A, Parra A, et al. Possible role for vascular cell proliferation in cerebral vasospasm after subarachnoid hemorrhage. *Stroke.* 2003; 34: 427-433.
 - 141 Hendryk S, Jarzab B, Josko J. Increase of the IL-1 beta and IL-6 levels in CSF in patients with vasospasm following aneurysmal SAH. *Neuro Endocrinol Lett.* 2004; 25: 141-147.
 - 142 Polin RS, Bavbek M, Shaffrey ME, et al. Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. *J Neurosurg.* 1998; 89: 559-567.
 - 143 Fassbender K, Hodapp B, Rossol S, et al. Endothelin-1 in subarachnoid hemorrhage: An acute-phase reactant produced by cerebrospinal fluid leukocytes. *Stroke.* 2000; 31: 2971-2975.
 - 144 Nissen JJ, Mantle D, Gregson B, et al. Serum concentration of adhesion molecules in patients with delayed ischaemic neurological deficit after aneurysmal subarachnoid haemorrhage: the immunoglobulin and selectin superfamilies. *J Neurol Neurosurg Psychiatry.* 2001; 71: 329-333.
 - 145 Mori T, Nagata K, Town T, et al. Intracisternal increase of superoxide anion production in a canine subarachnoid hemorrhage model. *Stroke.* 2001; 32: 636-642.
 - 146 Ng WH, Moochhala S, Yeo TT, et al. Nitric oxide and subarachnoid hemorrhage: elevated level in cerebrospinal fluid and their implications. *Neurosurgery.* 2001; 49: 622-626; discussion 626-627.
 - 147 Sakowitz OW, Wolfrum S, Sarrafzadeh AS, et al. Temporal profiles of extracellular nitric oxide metabolites following aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl.* 2002; 81: 351-354.
 - 148 Yoshimoto Y, Tanaka Y, Hoya K. Acute systemic inflammatory response syndrome in subarachnoid hemorrhage. *Stroke.* 2001; 32: 1989-1993.
 - 149 Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. *Neurology.* 2001; 56: 1299-1304.
 - 150 Hughes JT, Schianchi PM. Cerebral artery spasm. A histological study at necropsy of the blood vessels in cases of subarachnoid hemorrhage. *J Neurosurg.* 1978; 48: 515-525.
 - 151 Iuliano BA, Pluta RM, Jung C, et al. Endothelial dysfunction in a primate model of cerebral vasospasm. *J Neurosurg.* 2004; 100: 287-294.
 - 152 Smith RR, Clower BR, Grotendorst GM, et al. Arterial wall changes in early human vasospasm. *Neurosurgery.* 1985; 16: 171-176.
 - 153 Zubkov AY, Tibbs RE, Aoki K, et al. Morphological changes of cerebral penetrating arteries in a canine double hemorrhage model. *Surg Neurol.* 2000; 54: 212-219; discussion 219-220.
 - 154 Findlay JM, Weir BK, Kanamaru K, et al. Arterial wall changes in cerebral vasospasm. *Neurosurgery.* 1989; 25: 736-745; discussion 745-736.
 - 155 McGirt MJ, Lynch JR, Blessing R, et al. Serum von Willebrand factor, matrix metalloproteinase-9, and vascular endothelial growth factor levels predict the onset of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurgery.* 2002; 51: 1128-1134; discussion 1134-1125.
 - 156 Frijns CJ, Rinkel GJ, Castiglione D, et al. Endothelial cell activation after subarachnoid hemorrhage. *Neurosurgery.* 2002; 50: 1223-1229; discussion 1229-1230.

- 157 Doczi T. The pathogenetic and prognostic significance of blood-brain barrier damage at the acute stage of aneurysmal subarachnoid haemorrhage. Clinical and experimental studies. *Acta Neurochir (Wien)*. 1985; 77: 110-132.
- 158 Doczi T, Joo F, Adam G, et al. Blood-brain barrier damage during the acute stage of subarachnoid hemorrhage, as exemplified by a new animal model. *Neurosurgery*. 1986; 18: 733-739.
- 159 Sehba FA, Mostafa G, Knopman J, et al. Acute alterations in microvascular basal lamina after subarachnoid hemorrhage. *J Neurosurg*. 2004; 101: 633-640.
- 160 Clower BR, Yoshioka J, Honma T, et al. Blood platelets and early intimal changes in cerebral arteries following experimental subarachnoid hemorrhage. In: Wilkins RL ed. *Cerebral vasospasm*. New York: Raven Press; 1988. p. 334-342.
- 161 Keimowitz RM, Annis BL. Disseminated intravascular coagulation associated with massive brain injury. *J Neurosurg*. 1973; 39: 178-180.
- 162 Goodnight SH, Kenoyer G, Rapaport SI, et al. Defibrination after brain-tissue destruction: A serious complication of head injury. *N Engl J Med*. 1974; 290: 1043-1047.
- 163 Drake TA, Morrissey JH, Edgington TS. Selective cellular expression of tissue factor in human tissues. Implications for disorders of hemostasis and thrombosis. *Am J Pathol*. 1989; 134: 1087-1097.
- 164 Fleck RA, Rao LV, Rapaport SI, et al. Localization of human tissue factor antigen by immunostaining with monospecific, polyclonal anti-human tissue factor antibody. *Thromb Res*. 1990; 59: 421-437.
- 165 Eddleston M, de la Torre JC, Oldstone MB, et al. Astrocytes are the primary source of tissue factor in the murine central nervous system. A role for astrocytes in cerebral hemostasis. *J Clin Invest*. 1993; 92: 349-358.
- 166 Day SM, Reeve JL, Pedersen B, et al. Macrovascular thrombosis is driven by tissue factor derived primarily from the blood vessel wall. *Blood*. 2005; 105: 192-198.
- 167 Vallet B, Wiel E. Endothelial cell dysfunction and coagulation. *Crit Care Med*. 2001; 29: S36-41.
- 168 Edelberg JM, Christie PD, Rosenberg RD. Regulation of vascular bed-specific prothrombotic potential. *Circ Res*. 2001; 89: 117-124.
- 169 Stein SC, Smith DH. Coagulopathy in traumatic brain injury. *Neurocrit Care*. 2004; 1: 479-488.
- 170 Ettinger MG. Coagulation abnormalities in subarachnoid hemorrhage. *Stroke*. 1970; 1: 139-142.
- 171 Kasuya H, Shimizu T, Okada T, et al. Activation of the coagulation system in the subarachnoid space after subarachnoid haemorrhage: serial measurement of fibrinogen, plasminogen activator and bradykinin in cerebrospinal fluid and plasma in patients with subarachnoid haemorrhage. *Acta Neurochir (Wien)*. 1988; 91: 120-125.
- 172 Fujii Y. Thrombin-antithrombin complex levels in subarachnoid hemorrhage. *J Neurosurg*. 1998; 88: 614-615.
- 173 Itoyama Y, Fujioka S, Takaki S, et al. Significance of elevated thrombin-antithrombin III complex and plasmin-alpha 2-plasmin inhibitor complex in the acute stage of nontraumatic subarachnoid hemorrhage. *Neurosurgery*. 1994; 35: 1055-1060.
- 174 Suzuki M, Kudo A, Otawara Y, et al. Extrinsic pathway of blood coagulation and thrombin in the cerebrospinal fluid after subarachnoid hemorrhage. *Neurosurgery*. 1999; 44: 487-493; discussion 493-484.
- 175 Ohkuma H, Suzuki S, Kimura M, et al. Role of platelet function in symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke*. 1991; 22: 854-859.
- 176 Tsementzis SA, Honan WP, Nightingale S, et al. Fibrinolytic activity after subarachnoid haemorrhage and the effect of tranexamic acid. *Acta Neurochir (Wien)*. 1990; 103: 116-121.
- 177 Suzuki M, Kudo A, Otawara Y, et al. Fibrinolytic activity in the CSF and blood following subarachnoid haemorrhage. *Acta Neurochir (Wien)*. 1997; 139: 1152-1154.
- 178 Antovic J, Bakic M, Zivkovic M, et al. Blood coagulation and fibrinolysis in acute ischaemic and haemorrhagic (intracerebral and subarachnoid haemorrhage) stroke: does decreased plasmin inhibitor indicate increased fibrinolysis in subarachnoid haemorrhage compared to other types of stroke? *Scand J Clin Lab Invest*. 2002; 62: 195-199.
- 179 Denton IC, Robertson JT, Dugdale M. An assessment of early platelet activity in experimental subarachnoid hemorrhage and middle cerebral artery thrombosis in the cat. *Stroke*. 1971; 2: 268-272.
- 180 Hirashima Y, Hamada H, Kurimoto M, et al. Decrease in platelet count as an independent risk factor for symptomatic vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2005; 102: 882-887.
- 181 Fujii Y, Takeuchi S, Sasaki O, et al. Serial changes of hemostasis in aneurysmal subarachnoid hemorrhage with special reference to delayed ischemic neurological deficits. *J Neurosurg*. 1997; 86: 594-602.
- 182 Peltonen S, Juvela S, Kaste M, et al. Hemostasis and fibrinolysis activation after subarachnoid hemorrhage. *J Neurosurg*. 1997; 87: 207-214.
- 183 Ilveskero S, Juvela S, Siironen J, et al. D-dimer predicts outcome after aneurysmal subarachnoid hemorrhage: no effect of thromboprophylaxis on coagulation activity. *Neurosurgery*. 2005; 57: 16-24; discussion 16-24.
- 184 Sehba FA, Mostafa G, Friedrich V, Jr, et al. Acute microvascular platelet aggregation after subarachnoid hemorrhage. *J Neurosurg*. 2005; 102: 1094-1100.
- 185 Tani E, Yamagata S, Ito Y. Intercellular granules and vesicles in prolonged cerebral vasospasm. *J Neurosurg*. 1978; 48: 179-189.
- 186 Parra A, McGirt MJ, Sheng H, et al. Mouse model of subarachnoid hemorrhage associated cerebral vasospasm: methodological analysis. *Neurol Res*. 2002; 24: 510-516.
- 187 Suzuki S, Suzuki M, Iwabuchi T, et al. Role of multiple cerebral microthrombosis in symptomatic cerebral vasospasm: with a case report. *Neurosurgery*. 1983; 13: 199-203.
- 188 Suzuki S, Kimura M, Souma M, et al. Cerebral microthrombosis in symptomatic cerebral vasospasm--a quantitative histological study in autopsy cases. *Neurol Med Chir (Tokyo)*. 1990; 30: 309-316.
- 189 Klotzsch C, Nahser HC, Henkes H, et al. Detection of microemboli distal to cerebral aneurysms before and after therapeutic embolization. *Am J Neuroradiol*. 1998; 19: 1315-1318.
- 190 Giller CA, Giller AM, Landreneau F. Detection of emboli after surgery for intracerebral aneurysms. *Neurosurgery*. 1998; 42: 490-493; discussion 493-494.
- 191 Romano JG, Forteza AM, Concha M, et al. Detection of microemboli by transcranial Doppler ultrasonography in aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2002; 50: 1026-1030; discussion 1030-1021.
- 192 Rordorf G, Koroshetz WJ, Copen WA, et al. Diffusion- and perfusion-weighted imaging in vasospasm after subarachnoid hemorrhage. *Stroke*. 1999; 30: 599-605.
- 193 Kaufman HH, Mattson JC. Coagulopathy in head injury. In: Becker DPPJ ed. *Central nervous system trauma status report*. Bethesda: National Institute of Neurological and Communicative Disorders and Stroke; 1985. p. 187-206.
- 194 Yanamoto H, Kikuchi H, Okamoto S, et al. Preventive effect of synthetic serine protease inhibitor, FUT-175, on cerebral vasospasm in rabbits. *Neurosurgery*. 1992; 30: 351-356; discussion 356-357.
- 195 Yanamoto H, Kikuchi H, Okamoto S. Effects of protease inhibitor and immunosuppressant on cerebral vasospasm after subarachnoid hemorrhage in rabbits. *Surg Neurol*. 1994; 42: 382-387.

- 196 Juvela S. Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 1995; 82: 945-952.
- 197 Niemi T, Tanskanen P, Taxell C, et al. Effects of non-steroidal anti-inflammatory drugs on hemostasis in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol.* 1999; 11: 188-194.
- 198 Thai QA, Oshiro EM, Tamargo RJ. Inhibition of experimental vasospasm in rats with the periadventitial administration of ibuprofen using controlled-release polymers. *Stroke.* 1999; 30: 140-147.
- 199 Philippon J, Grob R, Dagreou F, et al. Prevention of vasospasm in subarachnoid haemorrhage. A controlled study with nimodipine. *Acta Neurochir (Wien).* 1986; 82: 110-114.
- 200 Seiler RW, Grolimund P, Zurbrugg HR. Evaluation of the calcium-antagonist nimodipine for the prevention of vasospasm after aneurysmal subarachnoid haemorrhage. A prospective transcranial Doppler ultrasound study. *Acta Neurochir (Wien).* 1987; 85: 7-16.
- 201 Roos YB, Levi M, Carroll TA, et al. Nimodipine increases fibrinolytic activity in patients with aneurysmal subarachnoid hemorrhage. *Stroke.* 2001; 32: 1860-1862.
- 202 Nishida K, Markey SP. Nicardipine and MK-801 attenuate platelet-activating factor increases following cerebral ischemia-reperfusion in gerbils. *Brain Res.* 1996; 733: 203-210.
- 203 Parra A, Kreiter KT, Williams S, et al. Effect of prior statin use on functional outcome and delayed vasospasm after acute aneurysmal subarachnoid hemorrhage: a matched controlled cohort study. *Neurosurgery.* 2005; 56: 476-484; discussion 476-484.
- 204 Endres M, Laufs U. Effects of statins on endothelium and signaling mechanisms. *Stroke.* 2004; 35: 2708-2711.
- 205 Lu D, Mahmood A, Goussev A, et al. Atorvastatin reduction of intravascular thrombosis, increase in cerebral microvascular patency and integrity, and enhancement of spatial learning in rats subjected to traumatic brain injury. *J Neurosurg.* 2004; 101: 813-821.
- 206 Lu D, Goussev A, Chen J, et al. Atorvastatin reduces neurological deficit and increases synaptogenesis, angiogenesis, and neuronal survival in rats subjected to traumatic brain injury. *J Neurotrauma.* 2004; 21: 21-32.
- 207 Tokiyoshi K, Ohnishi T, Nii Y. Efficacy and toxicity of thromboxane synthetase inhibitor for cerebral vasospasm after subarachnoid hemorrhage. *Surg Neurol.* 1991; 36: 112-118.
- 208 Abe Y, Kasuya H, Suzuki S, et al. Effect of a platelet-activating factor antagonist, E5880, on cerebrovasospasm following subarachnoid hemorrhage in a canine double-hemorrhage model. *Eur J Pharmacol.* 2002; 455: 127-133.
- 209 Chow M, Dumont AS, Kassell NF. Endothelin receptor antagonists and cerebral vasospasm: an update. *Neurosurgery.* 2002; 51: 1333-1341; discussion 1342.
- 210 Levi M, Keller TT, van Gorp E, et al. Infection and inflammation and the coagulation system. *Cardiovasc Res.* 2003; 60: 26-39.
- 211 Levi M, ten Cate H, van der Poll T. Endothelium: interface between coagulation and inflammation. *Crit Care Med.* 2002; 30: S220-224.
- 212 Gando S, Kameue T, Matsuda N, et al. Combined activation of coagulation and inflammation has an important role in multiple organ dysfunction and poor outcome after severe trauma. *Thromb Haemost.* 2002; 88: 943-949.
- 213 Asada M, Kong J, Nakamura M, et al. Thrombolytic therapy with tissue plasminogen activator for prevention of vasospasm in experimental subarachnoid hemorrhage: its efficacy and problems. *Neurol Res.* 1996; 18: 342-344.
- 214 Hamada J, Kai Y, Morioka M, et al. Effect on cerebral vasospasm of coil embolization followed by microcatheter intrathecal urokinase infusion into the cisterna magna: a prospective randomized study. *Stroke.* 2003; 34: 2549-2554.
- 215 Roos YB, Rinkel GJ, Vermeulen M, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2000: CD001245.
- 216 Rordorf G, Bellon RJ, Budzik RE, Jr, et al. Silent thromboembolic events associated with the treatment of unruptured cerebral aneurysms by use of Guglielmi detachable coils: prospective study applying diffusion-weighted imaging. *Am J Neuroradiol.* 2001; 22: 5-10.
- 217 Soeda A, Sakai N, Sakai H, et al. Thromboembolic events associated with Guglielmi detachable coil embolization of asymptomatic cerebral aneurysms: evaluation of 66 consecutive cases with use of diffusion-weighted MR imaging. *Am J Neuroradiol.* 2003; 24: 127-132.
- 218 Albayram S, Selcuk D. Thromboembolic events associated with Guglielmi detachable coil embolization of asymptomatic cerebral aneurysms: evaluation of 66 consecutive cases with use of diffusion-weighted MR imaging. *Am J Neuroradiol.* 2004; 25: 159-160; author reply 160.
- 219 Soeda A, Sakai N, Murao K, et al. Thromboembolic events associated with Guglielmi detachable coil embolization with use of diffusion-weighted MR imaging. Part II. Detection of the microemboli proximal to cerebral aneurysm. *Am J Neuroradiol.* 2003; 24: 2035-2038.
- 220 Dorsch NW, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage Part I: Incidence and effects. *J Clin Neurosci.* 1994; 1: 19-26.
- 221 Kassell NF, Sasaki T, Colohan AR, et al. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke.* 1985; 16: 562-572.
- 222 Weir B, Grace M, Hansen J, et al. Time course of vasospasm in man. *J Neurosurg.* 1978; 48: 173-178.
- 223 van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet.* 2007; 369: 306-318.
- 224 Jaeger M, Schuhmann MU, Soehle M, et al. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke.* 2007; 38: 981-986.
- 225 Vergouwen MD, Vermeulen M, Coert BA, et al. Microthrombosis after aneurysmal subarachnoid hemorrhage: an additional explanation for delayed cerebral ischemia. *J Cereb Blood Flow Metab.* 2008; 28: 1761-1770.
- 226 Kosnik EJ, Hunt WE. Postoperative hypertension in the management of patients with intracranial arterial aneurysms. *J Neurosurg.* 1976; 45: 148-154.
- 227 Sen J, Belli A, Albon H, et al. Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. *Lancet Neurol.* 2003; 2: 614-621.
- 228 Egge A, Waterloo K, Sjöholm H, et al. Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. *Neurosurgery.* 2001; 49: 593-605; discussion 605-596.
- 229 Dankbaar JW, Slooter AJ, Rinkel GJ, et al. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review. *Crit Care.* 2010; 14: R23.
- 230 van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain.* 2001; 124: 249-278.
- 231 Shimoda M, Oda S, Tsugane R, et al. Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. *J Neurosurg.* 1993; 78: 423-429.
- 232 Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2007: CD000277.

- 233 Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis.* 2013; 35: 93-112.
- 234 Connolly ES, Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2012; 43: 1711-1737.
- 235 Vergouwen MD, Meijers JC, Geskus RB, et al. Biologic effects of simvastatin in patients with aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled randomized trial. *J Cereb Blood Flow Metab.* 2009; 29: 1444-1453.
- 236 Vergouwen MD, de Haan RJ, Vermeulen M, et al. Effect of statin treatment on vasospasm, delayed cerebral ischemia, and functional outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis update. *Stroke.* 2010; 41: e47-52.
- 237 Dorhout Mees SM, Algra A, Vandertop WP, et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet.* 2012; 380: 44-49.
- 238 Rabinstein AA, Weigand S, Atkinson JL, et al. Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke.* 2005; 36: 992-997.
- 239 Schmidt JM, Wartenberg KE, Fernandez A, et al. Frequency and clinical impact of asymptomatic cerebral infarction due to vasospasm after subarachnoid hemorrhage. *J Neurosurg.* 2008; 109: 1052-1059.
- 240 Shimoda M, Takeuchi M, Tominaga J, et al. Asymptomatic versus symptomatic infarcts from vasospasm in patients with subarachnoid hemorrhage: serial magnetic resonance imaging. *Neurosurgery.* 2001; 49: 1341-1348; discussion 1348-1350.
- 241 Mayberg MR, Batjer HH, Dacey R, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke.* 1994; 25: 2315-2328.

Jaroslav Krejza, MD, PhD
Department of Diagnostic Radiology
of the University of Maryland
Division of Clinical Research
22 South Greene Street
Baltimore, Maryland 21201
E-mail: jkrejza@umm.edu; jkrejza@me.com