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Posterior circulation stroke and animal models

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1. ABSTRACT

The posterior circulation is part of the brain circulation that is subject to stroke. Strokes which involve the posterior circulation account for approximately 25% of all ischemic strokes, and about 10-20% of all hemorrhagic strokes. While the mortality rate from ischemic strokes in posterior circulation could be as low as 4%, the cerebellar and pontine hemorrhages carry a mortality rate close to 20% and 60%, respectively mainly due to brainstem compression secondary to edema or from direct parenchymal damage to vital cardio-respiratory centers. There are very few therapies geared towards neuroprotection or for reduction of edema in the posterior circulation. In fact, most treatments for anterior circulation stroke are commonly used for the posterior circulation, without an adequate study of the benefits and drawbacks. Since multiple neurovascular differences exist between these two circulations, this would imply that additional studies are needed to refine the clinical treatments in the posterior region. This review summarizes the existing animal models for posterior circulation stroke or vascular insufficiency, and discusses the anatomical, histological, neuronal, neurobehavioral and neurovascular differences at the hindbrain in comparison to the forebrain.

2. INTRODUCTION

Stroke is the third leading cause of death in North America with an estimated incidence of 700,000. This is number is predicted to increase with growth and age of the population (1, 2). Stroke prognosis relates to the size and location of the hematoma or infarct. Therefore, since the brainstem and cerebellum are confined to much smaller space than the cerebral hemispheres, and include several life-sustaining neural tracts, the effects of infarction, bleeding and edema can lead to significant morbidity or mortality to these patients.

3. PROGNOSIS AND ETIOLOGY OF POSTERIOR STROKE

3.1. Vertebrobasilar transient ischemic attacks (VTIA)

Vertebrobasilar transient ischemic attacks (VTIA) are defined as completely reversible focal neurologic deficits lasting less than 24 hours. These are located in the posterior circulation and are caused by transient episodes of arterial narrowing. The median duration of vertebrobasilar TIAs is about half the duration of those in the carotid territory, at 8 minutes and 14 minutes, respectively (3).

The likelihood of stroke over 5 years after a VTIA has been estimated to be 22-35% (4, 5). However, since the prognosis of VTIAs has been conceived by many to be more benign than carotid based TIAs (6-11), these patients have tended to be investigated less thoroughly, and therefore received less aggressive preventative treatment (12-14). However, when Flossmann *et al* (12) performed a systematic review of 16839 patients presenting with either vertebrobasilar or carotid territory TIAs, they found no difference in rates of consequent stroke or death between the two groups. However, the risk of subsequent stroke was probably higher in the acute phase of VTIA, as compared to the carotid territory. This suggests against a difference between the investigative rigors and preventative measures applied to these two different types of TIAs.

3.2. Posterior circulation ischemic strokes (PCIS)

Approximately 25% of all ischemic strokes are located in the posterior circulation (15, 16). Prognosis is related to the site of vessel occlusion. Therefore, the small lacunar posterior circulation ischemic strokes (PCIS) generally have good a prognosis as long as vital cardiorespiratory centers are intact, while the large vessel occlusions, such as acute basilar artery or intracranial vertebral artery occlusions, have a much worse prognosis (17).

Vertebrobasilar strokes are usually caused by thrombi or emboli to the vertebral or basilar arteries, or less commonly may occur from vertebral artery dissection, which typically originates at the C1-2 vertebral level, most commonly secondary to trauma (3). 129 patients with posterior circulation ischemic stroke (PCIS) from the Oxfordshire Community Stroke Project had a 6-8 month mortality of 14% and major disability of 18% (15). However, a more recent prospective study with 407 PCIS patents at the New England Medical Centre Posterior Circulation Registry (NEMC- PCR), demonstrated an overall mortality of only 3.6%, with only 18% of patients having major disability (18). Furthermore, of the 87 patients with basilar artery occlusion in the NEMC- PCR, there was an overall poor outcome in 28% of patients and this increased to 58% in patients with proven cardiac or vertebral embolism (19). In comparison, however, Lindsberg and Mattle (20) performed a systematic analysis of 10 published case series about basilar artery occlusion which included 344 patients, and the overall reported death or dependency rate was 76%; this was much higher than the NEMC- PCR (20). However, the former likely had an element of selection bias for a greater proportion of severe cases, whereas the latter included many more out-patients or minor stroke patients.

3.3. Posterior circulation hemorrhagic strokes (PCHS)

Approximately 15% of all strokes are due to primary or secondary intracerebral hemorrhage (2, 21), and of these, 5-10% will occur in the cerebellum, and 5-9% in the pons (22). Although 80-90% of primary intracerebral hemorrhages are caused by either amyloid angiopathy or hypertensive arteriosclerosis (23) with respect to the posterior circulation, cerebrovascular damage from uncontrolled hypertension is the most important etiologic factor leading to the hemorrhages (22). Less common causes of secondary PCHS include neoplasia, coagulopathy, and vascular anomalies such as: AVMs, aneurysms, cavernomas, dural arteriovenous fistulas and venous malformations (22). Mortality depends both on hematoma location and bleeding volume. Generally speaking, primary pontine hemorrhage carries mortality near 60% (24) and around 20-30% for hemorrhages in the cerebellum (25).

4. VASCULAR ANATOMY OF THE POSTERIOR CIRCULATION

4.1. Vessel nomenclature and distribution

The posterior circulation is supplied by two vertebral arteries and basilar artery, and extends from the caudal medulla to the occipital lobes. It provides blood flow to the occipital lobes, inferior thalamus, cerebellum, midbrain, pons and medulla (17). At the junction between the medulla and pons, the two vertebral arteries fuse to form the basilar artery (26), which courses along the anterior aspect of the pons and mesencephalon, releasing dorsolateral superficial branches to the cerebellum and deep branches to the brainstem (27). The basilar artery ultimately terminates at the basilar tip within the mesencephalic cistern, then bifurcates into the paired posterior cerebral arteries (PCA). The PCAs first course ventral and lateral to anastomose with the posterior communicating arteries (PComA), then dorsal and lateral to supply parts of the occipital and temporal cortex.

The deep basilar artery branches can be subdivided into paramedian and circumferential, the former entering the brainstem along the anterior aspect, and the latter supplying the lateral side. At the basilar tip, the perforator branches supply parts of the diencephalon.

Table 1. Combined vertebrobasilar ischemic syndromes by anatomical location

Anatomy	Tasks	Vascular Distribution	Syndrome(s)	Ipsilateral symptoms	Contralateral symptoms
Thalamus	Motor and sensory integration	Posterior cerebral artery	Dejerine-Roussy	None	Upper and lower limb loss of pain, temperature, light touch and proprioceptive sensation. Upper and lower limb pain syndrome
Occipital and Inferior-medial temporal lobe	Motor and sensory integration	Posterior cerebral artery	Anton, Balint	Loss of: vision, voluntary eye movements, visual-motor coordination, interpretation of visual objects. Denial of blindness.	Loss of vision, denial of blindness
Midbrain	Movement, sensation and consciousness	Posterior cerebral artery	Weber, Benedikt, Claude, Parinaud	Oculomotor nerve palsy, fixed pupils, gaze and accommodation paralysis	Upper and lower limb hemipalagia, tremor, cerebellar ataxia, cortical spinal tract deficits
Pons	Movement, sensation and consciousness	Basilar artery, Anterior inferior cerebellar artery	Foville, Millard-Gubler, Marie-foix, Locked-in syndrome	Upper and lower limb hemipalagia or ataxia, lateral gaze weakness, facial weakness, dysarthria	Upper and lower limb hemipalagia, loss of pain and temperature sensation
Medulla	Movement, sensation and consciousness	Vertebral artery, Posterior inferior cerebellar artery, Anterior Spinal artery	Wallenberg's (lateral medullary) syndrome, medial medullary syndrome	Vertigo, ataxia, loss of facial sensation, nystagmus, dysphagia, hoarseness, Horner's syndrome, tongue weakness	Upper and lower limb hemipalagia, loss of pain, temperature, light touch and proprioceptive sensation
Cerebellum	Maintains: muscle tone, coordination, gait, posture	Vertebral artery, Posterior inferior cerebellar artery	none	Anterior vermis: Truncal, leg, gait dystaxia Posterior vermis: Truncal ataxia	none

References: 3, 151, 152

Table 2. Vertebrobasilar ischemic symptoms by vascular distribution

Vascular Distribution	Anatomy	Ipsilateral symptoms	Contralateral symptoms
Posterior inferior cerebellar artery	Lateral medulla and inferior cerebellum	Loss of facial sensation, nystagmus, nausea, vomiting, diplopia, hiccups, Horner's syndrome, cranial nerves IX and X palsy, loss of sensation (truncal, upper and lower limbs)	Upper and lower limb loss of pain and temperature sensation
Anterior inferior cerebellar artery	Middle cerebellar peduncle, medulla, lateral inferior pons	Tinnitus, deafness, facial weakness, nausea, vomiting, lateral gaze paralysis, Horner's syndrome	Upper and lower limb loss of pain and temperature sensation
Lower basilar artery	Medial medulla	Hypoglossal nerve paralysis	Upper and lower limb hemipalagia, but facial sparing
Superior cerebellar artery	Middle and superior cerebellar peduncles	Nausea, vomiting, cerebellar ataxia, dysarthria	Facial and limb (upper and lower) loss of pain and temperature sensation, Horner's syndrome

References: 3, 151, 152

The dorsolateral (superficial) branches to the cerebellum consist of the superior cerebellar artery (SCA), anterior inferior cerebellar artery (AICA) and posterior inferior cerebellar artery (PICA). The SCA courses laterally from near the basilar tip above the superior cerebellar peduncles, to the ipsilateral cerebellar hemisphere and upper vermis. The AICA extends from the body of the basilar artery, over the middle cerebellar peduncles, to variable areas of cerebellar cortex. The PICA is a branch of the vertebral artery, which essentially completes cerebellar vascularization.

4.2. Collateral blood flow

The PCA has an abundance of collateral flow from the PComA, quadrigeminal plate SCA, leptomeninges, AICA and PICA (28, 29). Furthermore, there is collateral flow from the anterior circulation via the posterior pericallosal artery, anterior choroidal and superior temporal from the middle cerebral artery (30). Occasionally there are either duplications of the SCA or AICA, or they may divide near their origin (31), theoretically impacting the collateral flow between PCA, cerebellum, and basilar artery.

Since the basilar artery is not a terminal vessel it may receive either anterograde flow from the paired vertebral arteries or retrograde flow from the PCA and PComA of the anterior circulation. Furthermore, the cerebellar arteries are anastomosed together by leptomeningeal interconnections similar to those of the cerebral pial anastomosis network, leading to another source of compensatory flow reversal into the basilar artery. In contrast, the paramedian, circumferential, and perforator branches of the basilar artery, are thought to be terminal vascular branches, leading to focal ischemia if occluded for a prolonged duration. This heterogeneity of differential vulnerability in the brain stem has led to the clinical identification of several PCIS syndromes (31) (Tables 1 and 2).

4.3. Anatomic variation

The two VAs may be of variable sizes ranging from double, to asymmetric, to single VA. Furthermore, the first segment of the PCA is in hemodynamic balance with the PComA, and there is an inverse relationship between their respective sizes (31).

Since the size of the basilar artery is directly

related to the amount of both upstream and downstream flow through the vessel, a hypoplastic output (PComA/PCA) or input (VA), would lead to less flow and consequently a smaller basilar artery. This could create an increased vulnerability for posterior circulation ischemic stroke (PCIS) secondary to the restricted endovascular lumen (32).

During upper basilar artery occlusion, the blood supply to the SCA, PCA and basilar bifurcation, occur through the reversal of flow through the PComAs (31). In fact, Steinberg *et al* (33) found that patients with larger PComAs were more tolerant to both basilar artery and first segmental PCA occlusions. The same concept applies to the collateral blood supply to the anterior circulation: Schomer *et al* (34) found that in patients with carotid artery occlusion, ischemic injury was attenuated in patients with PComAs greater than 1mm.

5. DIAGNOSTIC MODALITIES OF POSTERIOR STROKE

Duplex transcranial doppler ultrasound can assess the collateral blood flow from the circle of Willis during various degrees of vertebrobasilar occlusion and can assist in both the diagnosis and confirmation of post-treatment recanalization (3). With the exception of cerebellar infarction (35), the computed tomography (CT) scan visualizes ischemia in the posterior fossa poorly secondary to bony artifacts. However, the CT scan can visualize blood well, and is commonly performed prior to anticoagulant or thrombolytic therapy in vertebrobasilar stroke in order to investigate any bleeding (3). Compared to CT scan, however, the magnetic resonance imaging (MRI) visualizes the contents in the posterior fossa clearly and detects parenchymal ischemia fairly accurately (36). The addition of angiography to magnetic resonance imaging can further characterize any vertebrobasilar lesion and serve as a guide for a formal angiography procedure (3). In fact, angiography is the gold standard to demonstrate the location of arterial occlusion or stenosis and may be performed also in conjunction with CT, stenting, percutaneous transluminal angioplasty or intra-arterial thrombolysis (3, 31).

It should be recommended for cardiac function to be assessed with echocardiography in any patient with high probability cardiogenic embolism (37). In fact, although a significant number of vertebrobasilar infarcts are cardioembolic, any etiologic cause of ischemia extending to the medulla can cause cardiac abnormalities, and this must be investigated and cared for appropriately (38).

6. THERAPEUTICS FOR POSTERIOR STROKE

6.1. Aspirin compared to heparin

Both the first International Stroke Trial (IST-1) (39) and the Chinese Acute Stroke Trial (40) assessed the efficacy of aspirin given within 48 hours of stroke symptom onset. The results of the 3672 PCIS patients showed a small yet significant benefit with aspirin. However, IST-1 further assessed the efficacy of intra-venous heparin on 2228 PCIS patients and found no benefit with heparin. Therefore aspirin, but not heparin, is recommended to treat acute PCIS depending on the patient's clinical presentation and availability of more effective therapies such as intra-venous or intra-arterial thrombolysis.

6.2. Intra-venous thrombolysis (IVT)

Intravenous alteplase (tissue plasminogen activator) has been supported by randomized controlled clinical trials as an effective agent to treat acute ischemic stroke within 3 hours of symptom onset (41). To date, it is the only FDA approved treatment for stroke. However, there are several ongoing clinical trials with other intravenous thrombolytics beyond the 3 hour window. Nonetheless, a limitation to studies like NINDS (41) (National Institute of Neurological Disorders and Stroke) and ATLANTIS (42, 43) (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke), and others, is the apparently low a number of PCIS patients enrolled (17). In fact, the ECASS clinical trial (44) (European Cooperative Acute Stroke Study) totally excluded PCIS patients from the study. Therefore the potential risks and benefits of intravenous thrombolysis in PCIS stroke has not been sufficiently proven with randomized clinical trials. Future studies need to focus more on PCIS patients before conclusions could be accurately made regarding patient outcomes.

Basilar artery occlusion (BAO) is a type of PCIS that has a mortality of 85-95% without recanalization, even in the presence of anticoagulant or fibrinolytic therapy (45, 46). A few case series with IVT have shown some benefit in treating BAO, for example, in a study by Lindsberg *et al* (47), of 50 patients treated with IVT with proven basilar artery occlusion by magnetic resonance or catheter angiography, 52% had recanalization and 22% with a good outcome over at least 3 months, and symptomatic hemorrhage was only about 14%. Earlier case series by Hennerici (48) and Huemer (49), had similarly shown a good outcome in about 20% and hemorrhage in less than 10%, however the number of patients was low at 10 and 16, respectively.

6.3. Intra-arterial thrombolysis (IAT)

Lindsberg *et al* (50) reviewed published case series for IAT treatment of vertebrobasilar ischemic stroke. IAT had an approximate recanalization rate of 65%, good outcome in 24%, and intracranial hemorrhages in 8%. However, Arnold *et al* (51) published a case series of 40 patients receiving IAT during the first 12 hours since symptom onset, achieving recanalization in 80% and good outcome in 35%, and symptomatic hemorrhages in 5%.

In AUST (52)(Australian Urokinase Stroke Trial), the only randomized controlled clinical trial of IAT for PCIS, a total of 16 patients were enrolled to receive either IAT (urokinase) or anticoagulation, one out of eight in the control group compared to four of eight in the IAT group received a good outcome. However, the small number of patients limits the strength of this finding.

6.4. IAT compared to IVT

There are no randomized controlled trials comparing IAT with IVT, however, recently Lindsberg and Mattle (20) performed a systematic analysis of published case series between the IAT and IVT. The rate of death or dependency, survival, good outcome, and symptomatic hemorrhage were not significantly different between IAT and IVT. However, IAT (65%) had a higher rate of recanalization than IVT (53%).

Qureshi *et al* used a canine model of acute basilar artery thrombosis with 13 dogs (53), and administered half dose IAT and full dose IVT. Although the rates of recanalization were similar, the numbers of hemorrhages were greater in the IVT group. Therefore, the risks of hemorrhage might be greater in IVT therapy compared to IAT.

7. EXPERIMENTAL MODELS OF POSTERIOR CIRCULATION ISCHEMIA

Although there are an abundance of animal models to study supratentorial ischemia, far fewer have been developed for infratentorial infarcts. Nonetheless, similar methods have been employed in the posterior circulation to induce ischemia, including: endovascular suture, clipping, permanent sutured ligation, and photochemical or electrocautery occlusion of vertebrobasilar vessels. Experimental models have been developed for several species, including: rats, gerbils, cats, and dogs.

7.1. Rat model

By thoracotomy approach in rats, Henninger *et al* (54), exposed and ligated the left subclavian artery proximal and distal to the origin of the left vertebral artery, and a catheter was advanced into the vessel, through which autologous blood clots were injected. Lesions were distributed in the pons, medulla, midbrain and cerebellar hemispheres, yet 20% of animals had no detectable infarcts, nor did any posterior cerebral artery infarcts occur in any animals. Furthermore there was no mortality in this model, indicating an injury less dramatic than that in humans. A benefit is the avoidance of craniotomy, which allows the natural course of increased intracranial pressure to occur. However, a major drawback is the need for thoracotomy, which not only limits neurological testing, but may hinder the study of thrombolytic agents due to the risk of bleeding.

Similar to the ischemia and reperfusion model of middle cerebral occlusion in rats, Shiroyama *et al* (55) exposed part of the C2 vertebrae via an anterior cervical approach and removed part of the left transverse process, then exposed the vertebral artery. Next, they guided a silicone coated (6-0 nylon) suture into the vessel toward the basilar tip to induce the infarction. However, both infarct distributions and brain stem vascular parameters were widely variable, and the lack of reproducibility imposes a significant limitation upon this model.

Sekiguchi *et al* (56, 57) injected 900 microspheres into the right common carotid artery of rats and thereby caused widespread infarction in the brain. Most microspheres lodged in the neocortex, striatum, and hippocampus, and far less to the posterior circulation. However, embolic events were not only limited to the right cerebrum, but a few microspheres entered the cerebellum by way of the circle of Willis. Of these, most translocated ipsilateral to the site of injection, and far fewer to the contralateral cerebellum or the midbrain. Therefore, this model is limited by the lack of specific injury to the posterior circulation. Furthermore, it is not clear whether the cerebellar damage is exclusively due to the direct embolic events or secondary to other injury, since it has been shown that anterior circulation occlusion (middle cerebral artery) (58) or global ischemia (aortic clamping) (59, 60) could cause cerebellar neuronal damage also.

Using an occipital approach, Yao *et al* (61) cauterized the bilateral vertebral arteries at C1 foramina, and then decreased the mean arterial blood pressure (MAP) by approximately 50%. This induced hindbrain ischemia in spontaneously hypertensive (SH), but not normotensive rats. The spontaneously hypertensive rats had infratentorial ischemic metabolic changes including: decreased ATP, lactate and lactate/pyruvate ratios, whereas the normotensive rats had no such changes. However, the peripheral blood in these spontaneously hypertensive rats were acidic at 7.32 (normal approximately 7.43). Therefore, these acid-base changes could potentially confound the metabolic derangements and be the reason for the increased injury. In addition to this, although supratentorial cerebral blood flow was unchanged throughout the experiment in all groups, cerebellar blood flow decreased both in the spontaneously hypertensive and the normotensive rats. However, cerebellar blood flow was more greatly decreased in the spontaneously hypertensive group than the normotensive group.

Wojak *et al* (62) employed a ventral surgical dissection to expose the basilar artery through a transclival window, using a method that had been developed for three-vessel global ischemia in rats (63). They then coagulated the artery either at a single point between the circle of Willis and foramen magnum, or at two points caudal, rostral or straddling the AICA. Although none of the single point occlusions resulted in infarcts, the two point occlusions had variable results at best. The somatosensory evoked potentials (SEP) suppressed to less than half baseline during all occlusions, but SEPs normalized in all rats within 24 hours; and therefore, similar to humans, the utility for SEP is useful to confirm a vertebrobasilar occlusive event, but fails to correlate with extent of infarction by 24 hours.

In rats, Inui *et al* (64) employed rose bengal infusion, then with selective light transillumination, this led to focused lipid peroxidation of endothelial cells by oxygen free radicals and singlets, followed by adhesion and aggregation of platelets endoluminaly, thereby causing selective vascular occlusion. Furthermore, in a rat model of vertebrobasilar arterial insufficiency, Ueda *et al* (65) used a transclival approach to dissect a window between the occipital bone and atlas to place a clip around the right

vertebral artery. These models are discussed in greater detail under the section: "Vestibular and cochlear studies in rat models".

7.2. Gerbil model

The Mongolian gerbil has an incomplete circle of Willis because it lacks a posterior communicating artery (66). Instead, the basilar artery terminates as two superior cerebellar arteries, leading to deficient collateral circulation between the anterior and posterior circulations.

Yamada *et al* (67), created a model of ischemia and reperfusion in the hindbrain of Mongolian gerbils by placing a clip for 30 minutes at the origin of the basilar artery, near the vertebrobasilar junction. They had used an anterior transcervical approach to expose a space between the atlas and occipital bone to isolate the vessel. This model caused ischemia in the pons, cerebellum, medulla, midbrain and thalamus (india ink, microcarbon perfusion, delineated the ischemic borders). Carbon-14-iodoantipyrine measured local cerebral blood flow, and this demonstrated normalized flow immediately after reperfusion, but at 30 minutes the flow decreased like in ischemic reperfusion. But, they found that a portion of the sensorimotor cortex demonstrated decreased blood flow, which suggests a distant effect on forebrain blood flow autoregulation secondary to hindbrain reversible occlusion (topic discussed in greater depth in the Experimental vascular physiology section). However, the need to remove hindbrain boney encasements meant that intracranial pressures would not be ideally preserved, thus placing a limitation the use of this model.

Hata *et al* (68) produced a model of reversible extracranial vertebral artery occlusion in the Mongolian gerbil which avoided: craniectomy (preserving intracranial pressures), cerebral spinal fluid disruption (from cranial surgical approaches used in basilar artery ligation (67)), and systemic hypotension (61) (which may cause cerebral metabolic changes). Instead, using an anterior cervical incision they dissected through the longus colli muscle and exposed the bilateral vertebral arteries just proximal to their entry into the transverse foramina of cervical vertebrae and placed a silk suture around them. Shortly thereafter, 5 grams of tension were placed on the sutures to occlude the vertebral arteries for 30 minutes. The arrest of blood flow was determined by the lack of carbon black staining in the pons, medulla and cerebellum. The animals which received 5 minutes of ligation regained respiratory function and survived to at least a week; however animals receiving greater than 10 minutes of ligation died within 4 hours due to respiratory failure. The reversibility of brainstem auditory evoked potentials to the extent of brainstem ischemia has been well correlated in this model (69). Hematoxylin-eosin (HE) staining and microtubule-associated protein 2 (MAP 2) immunostaining have demonstrated bilateral lesions at the trigeminal motor, lateral vestibular, oculomotor nuclei, and other areas of the hindbrain. This heterogeneous pattern of staining indicates a differential vulnerability of neurons to ischemia in the hindbrain similar to what had been reported by others (topic discussed in greater depth in the Neuronal Differences Across the Tentorial Membrane section) (70).

7.3. Cat model

Nakahara *et al* (71) published a model of brainstem ischemia in cats induced by silicone rubber cylinders. After incising the right anterior chest, they exposed and catheterized the subclavian artery, then passed a catheter into the vertebral artery for angiography and embolization. Used Evans blue to assess changes in the blood brain barrier and neurological function was evaluated using a scale prepared by the authors, which included: level of consciousness, respiration, posture, motor disturbance, muscle tone, pain response, pupil dilation and eye movement, reaction to light, oculocephalic response, oculomotor palsy, swallowing and corneal reflex. Angiography confirmed embolization and the occlusion at the vertebrobasilar circulation and classified the occlusion according to the extent of filling defect distal to the embolus. Approximately 58% of cats had emboli reaching the basilar artery, most toward the distal aspect and less proximally. Animals with a complete occlusion had dye extravasation caudal to the occlusion and demonstrated coma, tetraplegia, apnea and swallowing disturbance; these did not survive past two days. Those with incomplete occlusion survived for three days, with some dye extravasation only near the site of occlusion. The lack of infarct reproducibility from variability in embolus location limits this model to study stroke.

7.4. Dog model

Around 40 years ago, a few canine studies used craniotomy approach to expose the vertebrobasilar arteries and place a ligature (72), clip (73), and inject iron fillings (74) or air emboli (75). However, these methods were highly invasive, led to leakage of cerebrospinal fluid, and likely secondary cortical injury due to the operation itself (72, 73). Furthermore, the iron fillings and air emboli led to variable ischemic insults and excessive rates of mortality (74, 75). Therefore, at that time, the clinical scenarios of ischemia, reperfusion, and increased intracranial pressure had not been sufficiently replicated in an animal model.

Then, Kuwabara *et al* (76) used an infra-temporal surgical approach to expose the interpeduncular cistern and occluded 8-10 perforating arteries extending from the posterior cerebral arteries to the rostral brainstem. Infarction developed in the posterior thalamus, subthalamus, midbrain and upper pons. The animals survived for over a week and displayed the following neurologic symptoms: disturbed consciousness, tetraparesis oculomotor paralysis, respiratory abnormalities, bradycardia and arrhythmia; these are similar to those symptoms seen in human vertebrobasilar stroke. This model is useful to study the pathophysiology of permanent occlusive stroke in the upper vertebrobasilar system, paramedian thalamic or midbrain infarcts. However the lack of reperfusion injury limits the clinical relevance of this model.

During neurosurgical treatment of complex vertebrobasilar aneurisms, neurosurgeons may interrupt the blood supply to the brain stem for a short period of time.

This leads to ischemia and reperfusion, similar to that of short-lived occlusive vertebrobasilar emboli or thrombus. Therefore, to study the neuroprotective effects of therapeutic agents in the posterior circulation, Guo *et al* (77) developed a model of brain stem ischemia and reperfusion in a dog model. Using an anterior cervical approach, they performed a bone resection of the clivus from the anterior rim of the foramen magnum to the anterior arch of C1. Then exposed the basilar artery from near the tip, down to the bilateral vertebral arteries and the ventral spinal artery.

They isolated the anterior and posterior circulations by embolizing the bilateral posterior communicating arteries and superior cerebellar arteries with cyanoacrylate glue by a catheter inserted just proximal to the basilar artery bifurcation. Then reversible brain stem ischemia and reperfusion was achieved by temporary clipping of both vertebral arteries and the ventral spinal artery. Proximal basilar artery perfusion pressure was monitored by catheter inserted between the junction of the left vertebral artery and the ventral spinal artery. Ischemia was confirmed by several methods, including: decreased intra-operative regional cerebral blood flow (at the midbrain), decreased perfusion pressure (at the proximal basilar artery), flattened brain stem auditory evoked potentials (BAEPs), and postmortem evans dye leakage. At 10 minutes occlusions, BAEPs were fully reversed, however, by 20-30 minute occlusion, BAEPs were partially or completely diminished, without reversal. Therefore, they found that BAEP were a good index of occlusion duration in this model. However, cardiovascular and respiratory centers remained functional throughout the occlusion, suggesting a differential vulnerability compared to the auditory pathways, for example, which were not only more vulnerable to ischemia, but which also yielded the BAEP data. Furthermore, at the prolonged 30 minute occlusion, animals experienced delayed post-ischemic hypoperfusion. The clinical application of this model is limited by the gravity of the ischemic insult from the irreversible ischemia to the midbrain of the perforators, thereby making it impossible to assess functional neurological outcomes in the animals secondary to their vegetative state (77).

Qureshi *et al* (53) produced basilar artery thrombosis in a canine model of ischemia using a "superselective" catheterization technique, where they advanced a catheter up the femoral artery to the subclavian artery, and through the aorta. They then used "magnified road-mapping techniques" to guide the catheter from the right vertebral artery to the proximal basilar artery. Clots had been prepared with thrombin mixed with autologous blood, then injected into the basilar artery. This caused a basilar occlusive thrombus. Intravascular clot location and occlusion were confirmed by angiogram. Also, the infarct location and presence of hemorrhagic transformation were evaluated by T2 MRI. This model would allow testing of endovascular thrombolytic techniques and would be able to compare them to peripheral intravenous drug administration.

8. EXPERIMENTAL MODELS OF POSTERIOR CIRCULATION HEMORRHAGE

Scientific advancements of intracerebral hemorrhage have lagged behind ischemic strokes in a temporal fashion with regards to pathophysiologic mechanisms and therapeutic innovations. This has been even truer for the vertebrobasilar compared to the carotid based hemorrhages (78, 79).

8.1. Cat model

In the brainstem-cerebellum, several different animal studies had delineated neurophysiologic and neuroanatomic pathways, and studied posterior fossa mass lesion removal and cerebellopontine angle manipulations (78). However, the effects of intraparenchymal hemorrhage in the brain stem had not been previously studied until Chung *et al* (78), created a model of brainstem hemorrhage in cats. They injected 500 micro-liters of autologous blood into the basis pontis using a transtentorial approach. Neurological function was evaluated by brain stem auditory evoked responses (BAER) and these outcomes were compared between: no intervention, stereotactic aspiration with urokinase, and open surgical evacuation by longitudinal pontotomy (transoral-clival approach). Disappointingly, neither surgical evacuation nor stereotactic aspiration improved the BAER. However, other intervention techniques or mechanistic studies could prove some benefit to using this model in the future.

8.2. Rat model

Cossu *et al* (79, 80) created an animal model of cerebellar hemorrhage in rats. They performed an occipital craniectomy and exposed the posterior cerebellum. They then injected 50 micro-liters of autologous blood into the right cerebellum. This corresponds to an approximate 50 ml (cerebellar) hemorrhage in humans. Next, evaluated intracranial pressure through an intraventricular polythene catheter, and assessed changes in blood flow to the cerebrum and cerebellum by way of tissue hydrogen desaturation (clearance) method. Furthermore, tissue ischemia was assessed by the relative loss of enzyme histochemistry markers such as: glycogen phosphorylase and acetyl-cholinesterase. In the experimental group, both enzymes were decreased-to-absent for an approximate 1 mm rim around the clot, then returned to normal intensity with distance away from the clot. With respect to autoregulation, cerebellar blood flow decreased with the initial autologous blood injection, but returned to pre-injection values after 150 minutes. Interestingly, the adjacent pons had an overall decreased glycogen phosphorylase and acetyl-cholinesterase histochemistry, implying some degree of ischemia at a location distant from the site of hemorrhage. However, since blood flow was not assessed in the brainstem, the role of hypoperfusion in these adjacent structures needs further study in this model. Furthermore, the need for craniectomy in this model would lead to dissipation of any increased intracranial pressure (ICP), and thereby limit the clinical relevance.

9. VESTIBULAR AND COCHLEAR STUDIES IN RAT MODEL

Following a ventral approach to the middle ear, then avoiding the ossicles and tympanic membrane, Umemura *et al* (81) used rose bengal infusion followed by xenon light along the lateral aspect of the cochlea to cause photochemical occlusion (greater than 85%) to the cochlea of which was irreversible. The loss of action potential on the electrocochleogram confirmed the occlusion. This method caused permanent vascular occlusion of the cochlea. This would have the same end result as would have had an occlusion of cochlear branches off the vertebrobasilar circulation.

Then, Kohno *et al* (82) performed a vestibular vascular occlusion using the same photochemical method of the vestibule through the oval window, through a ventral approach to the middle ear after removal of the ossicles and tympanic membrane. Histological hair cell disintegration and edema of the macular and ampullar tissues confirmed the ischemia. The resulting vestibular dysfunction led to the nystagmus (toward intact side, confirmed by telemetric analysis) and also to an equilibrium dysfunction (verified by the presence of longitudinal axis rotation during swimming test). Therefore, this method successfully caused permanent vascular occlusion of the vestibule, similar to the product of occlusion of vestibular branches off the vertebrobasilar circulation.

Asai *et al* (83) used an anterior cervical dissection approach to the left tympanic bulla and skull base. They opened a bony window to expose either the proximal AICA or lateral boney wall of left cochlea and irreversibly occluded the AICA as it branched off the labyrinthine artery by the photochemical method (rose bengal infusion and xenon light illumination, as described earlier). Laser-Doppler flowmetry demonstrated a drop in cochlear blood flow (below 27-43% from baseline), and this led to dysfunction on the cochlear compound action potentials during an acute phase of ischemia (as determined by electrocochleography).

After using the rose bengal method to permanently occlude the left AICA through selective light transillumination, Inui *et al* (64) demonstrated in rats: positive vestibulospinal reflex, contralateral forelimb extension and ipsilateral limb flexion. The goal of their study was to test the extent to which the AICA vessels supply the cochlear and vestibular nuclei by using 4-iodo [N-methyl-14C] antipyrine (14C-IAP) to measure the (regional) blood flow to these nuclei after the occlusion. They found that the rate of blood-flow had decreased to one-third at the vestibular and to one-half at the cochlear nuclei, respectively. Both cochlear microphonics and summating potentials were found to decrease progressively with time from occlusion (electrocochleography method). However, since blood-flow never decreased below 15%, the action potentials remained intact in spite of irreversible left AICA occlusion. These results suggest an abundance of collateral circulation to the rat cochlea in spite of AICA occlusion.

Using 14C-IAP to measure the regional blood flow in the brainstem, Inui *et al* (84) performed either permanent left unilateral vertebral artery or AICA occlusion by rose bengal (photochemical) occlusion in two separate groups of rats. There wasn't a difference in blood flow between ipsilateral and contralateral cochlear sides after 30 minutes of left unilateral vertebral artery occlusion. For AICA occlusion, the cochlear nucleus had low flow at 30 minutes; however this converted back to normal flow by 2 hours. This suggests that following ischemia, there may some delayed volume of compensatory blood flow to the cochlear nucleus from the brain stem.

Ueda *et al* (65) placed a reversible clip to the right vertebral artery in a rat to create a model of vertebrobasilar arterial insufficiency (VBI). "Chemical" vascular control was manipulated by carbon dioxide inhalation, while autoregulatory vascular control was manipulated by femoral vein blood withdrawal to induce hypotension. Blood flow was evaluated by laser-Doppler flowmetry in the cochlea and brainstem. Their results showed that unilateral right vertebral arterial occlusion resulted in impaired blood flow autoregulation in both the brain stem and cochlea, but that carbon dioxide changes induced vasodilation in the brain stem only, not the cochlea. Therefore, vertebrobasilar dysautoregulation and the resulting hearing disturbances or vestibular disequilibrium, could occur secondary to hypoperfusion from unilateral vertebral artery occlusion, once confounded by blood pressure (e.g. orthostatic hypotension) or carbon dioxide level changes. This could account for the vertigo and hearing abnormalities seen in patients with VBI.

Ueda *et al* (85) performed unilateral vertebral artery occlusion using rose bengal photochemical occlusion in rats, and used laser-Doppler flowmetry to compare the effects on cochlear blood flow with or without induced hypotension. They found no difference between sides for cochlear blood flow secondary to either unilateral vertebral artery occlusion or venesection alone. However the combination of occlusion and systemic hypotension caused a bilateral decrease in cochlear blood flow, with the ipsilateral side blood flow decreased more than the contralateral cochlea. These results indicate that systemic hypotension may overcome the compensatory blood flow to the cochlea from the non-occluded vertebral artery or from the anterior circulation, and thereby lead to the vertigo seen in VBI patients.

In a rat model of vertebrobasilar arterial insufficiency, Ueda *et al* (86) used a trans-cervical approach to dissect a window between the occipital bone and atlas. They placed a reversible clip onto either the right vertebral artery or PICA. Then, nonradioactive microspheres were injected into the hindbrain circulation via the left ventricle, and the quantity of microspheres in the cochlea and semicircular canals, both ipsilateral and contralateral to the lesion, were used to evaluate blood flow post-mortem. Found no difference in blood flow between ipsilateral versus contralateral sides, nor any difference between the cochlea and semicircular canals. This is in contrast to their previous study which found a difference in

blood flow by laser-Doppler flowmetry method (65). This discrepancy could be accounted for by the fact that microspheres show total blood flow over time, whereas the laser-Doppler flowmetry provides an instantaneous temporal cross-section of blood-flow. Therefore, compensatory vascular mechanisms could lead to a balance of total blood flow following acute vertebrobasilar arterial insufficiency (VBI) in the hindbrain.

10. EXPERIMENTAL VASCULAR PHYSIOLOGY

10.1. Differential blood flow infarction thresholds

Using MR perfusion and diffusion technology, Bristow *et al* (87) determined that the cerebral blood flow thresholds for infarctions were 12ml/100g/minute for human gray matter, compared with 20ml/100g/minute for white matter. Since the hindbrain has a higher concentration of white matter than the forebrain, it is believed these hindbrain long-tracts could tolerate compromised blood flow secondary stroke better than the forebrain's predominately grey matter.

10.2. Perihematomal mitochondrial respiration

Kim-Han *et al* (88) tested mitochondrial respiration in perihematomal tissue of surgical specimens from hematoma evacuation surgery of 6 patients. Two of the patients had a hematoma in the cerebellum, and 4 from parietal or temporal lobe. They determined that perihematomal mitochondrial "state 3" oxygen consumption in ICH patients was 40% less than in controls. This oxygen consumption was essentially zero by 72 hours in the parietal or temporal lobe, but was abolished earlier in the cerebellum (by 6 hours). This suggests a differential mitochondrial vulnerability to perihematomal hypoperfusion across the tentorium. Therefore, perhaps compromised mitochondrial respiration could make the cerebellum more vulnerable compared to cortical regions. However, a greater number of patients and/or animal studies would be needed to further address this hypothesis.

10.3. Pediatric gender differences in posterior circulation autoregulation

Vavilala *et al* (89) used transcranial doppler (TCD) to compare the autoregulation of the anterior and posterior circulation in male and female children 10-16 years of age, using the "tilt test" method. Found that girls had greater basilar artery autoregulatory index, and higher flow velocities for both the middle cerebral and basilar arteries. In contrast, young boys had greater middle cerebral artery autoregulatory index and slower flow velocities for both arteries. Then, Tontisirin *et al* (90) examined even younger children ages 4 to 8 years old and also found higher flow velocities for both the middle cerebral and basilar arteries in young females, compared to the males. Furthermore, the middle cerebral artery has greater flow velocity than the basilar artery in both sexes. However, at these even younger ages, there were no gender differences in autoregulatory capacities between sexes or between the anterior and posterior circulations, as compared to the 10-16 year olds which did see a difference.

10.4. Posterior circulation autoregulation in normal humans

Cerebral autoregulation is the process in which blood vessels constrict or dilate in response to a wide range of mean arterial blood pressure (MABP) to maintain tissue perfusion at an optimal rate (91). Hypercapnia leads to cerebral vasodilatation (increased CBF), while hypocapnia leads to vasoconstriction (decreased CBF) in normal human brains (92, 93). In acute stroke, cerebral autoregulation is damaged, leading to an increased dependence of cerebral blood flow upon mean arterial pressure (94-96). The temporal and spatial differences of hampered cerebral autoregulation are not completely understood in stroke (97).

In normal human subjects Muller *et al* compared the blood flow of the basilar artery to the internal carotid, middle cerebral, posterior cerebral, and anterior cerebral artery blood flow using transcranial Doppler (TCD). They found no difference in cerebral hemodynamics between the different arteries (98). Rosengarten *et al* (99) compared the autoregulation of middle cerebral artery to the posterior cerebral artery in healthy human subjects, with the added challenge of a drop in blood pressure achieved by the "leg cuff test". They determined that the MCA recovery precedes the PCA by one second, but otherwise does not differ in either the time course of recovery in blood flow velocity.

During normoxia, Ito *et al* (100) investigated regional differences in vascular responses to partial pressure of carbon dioxide using positron emission tomography (PET) to compare cerebral blood flow (CBF) at: rest, hypercapnia and hypocapnia, in several regions in the brain. They found that the pons had a marked ability for both vasodilatation and vasoconstriction compared to most cortical areas. Furthermore, in comparison to the pons and cerebellum, most other cortical regions had diminished ability to vasodilate in response to hypercapnia. These results suggest that these hindbrain regions are more capable than some cortical regions to autoregulate blood flow in response to plasma levels of carbon dioxide. In contrast, Hida *et al* found no differences between the ventral medullary and cortical blood flow in response to hypocapnic, normocapnic and hypercapnic hyperventilation (101). Therefore, the medulla likely has less capacity to autoregulate as compared to the adjacent pons and cerebellum.

However, changes in plasma carbon dioxide might yield different vascular responses because Barrett *et al* (102) studied the effects of hypercarbia upon the two circulations using TCD, and found there to be similar vascular reserve potential between the anterior and posterior circulations. Similarly, Ogawa *et al* compared the basilar artery and middle cerebral artery using transcranial Doppler (TCD) under conditions of changing carbon dioxide levels and found no differences between the two circulations in these normal human subjects (103). Finally, Park *et al* (104) found that the dynamic autoregulatory response index (ARI) and carbon dioxide reactivity were

not different between the anterior and posterior circulations.

Interestingly, under sevoflurane anesthesia, Rozet *et al* (105) compared both cerebral autoregulation and cerebral reactivity to CO2 between the anterior and posterior circulations. They found that although flow velocity of the basilar artery was less than in the middle cerebral artery. Therefore, neither autoregulatory nor CO2 reactivity differences existed between the two circulations.

10.5. Posterior circulation autoregulation in normal animals

Merzeau *et al* (91) caused progressive hypotension in rats and compared blood flow in the cerebrum and cerebellum using laser Doppler flowmetry. They found that while the autoregulatory kinetics were maintained in the cerebrum over two different rates of blood pressure reduction, there was a progressive loss of autoregulatory efficacy in the cerebellum.

In cats, Sato *et al* (106) compared autoregulation and carbon dioxide responses by manipulating the mean arterial blood pressure (MABP) and CO2 levels, and measuring blood flow using the hydrogen clearance method in the cerebrum, cerebellum and spinal cord. Found that the cerebrum and spinal cord have greater susceptibility to pressure dependant ischemia than the cerebellum, which was relatively resistant.

De Bray *et al* compared the blood flow in the supratentorial and infratentorial compartments in rabbits under increasing intracranial pressure, using transcranial Doppler (TCD) (107). They found that the maximum amplitude of vasomotor activity occurred 30 seconds later in the basilar artery compared to the carotid siphon, indicating a differential effect of intracranial pressure on microvascular tone between the two circulations.

10.6 Autoregulation in humans during posterior circulation ischemic stroke or hypoperfusion

During hypoxia, Garbin *et al* (108) monitored blood flow velocities of the middle cerebral and basilar arteries with transcranial doppler (TCD) study. They found that the mean flow rate from the basilar arteries was significantly less than that of the middle cerebral arteries. Therefore, there may be differential capacities between brain regions, to maintain blood flow in the face of hypoperfusion.

Using TCD, Dawson *et al* (95, 109) compared both static and dynamic autoregulation over the middle cerebral artery territory. They found no difference between anterior and posterior circulation strokes within 96 hours and 1-2 weeks from stroke ictus. However all stroke patients, including those with posterior circulation ischemic stroke (PCIS), had compromised dynamic hemispheric cerebral autoregulation compared to the normal controls. This suggests the possibility of impaired supratentorial cerebral autoregulation secondary to a distant PCIS. However only 9 subjects had PCIS and this number of patients is too low to make any solid conclusions.

Then, Reinhard *et al* (110) determined that cerebral autoregulation was not significantly disturbed in early minor middle cerebral artery stroke, but was indeed impaired secondary to large middle cerebral artery infarcts (111). Taking these findings all together would suggest the possibility that distant PCIS have a greater impact on middle cerebral artery autoregulation impairment than minor local middle cerebral artery infarctions.

10.7. Autoregulation in humans with posterior circulation hemorrhagic stroke

Supratentorial cerebrovascular dysautoregulation secondary to cortical hemorrhagic stroke has been reported by several studies (112-119). However, in a small case series by Powers *et al* (120), of 14 patients with cortical hemorrhages, there were no significant changes in either global or peri-clot blood flow autoregulation over the range of 6 to 22 hours after onset of ICH symptoms. The role of cerebral dysautoregulation secondary to intracerebral hemorrhage is still uncertain. However, autoregulation in relation to infratentorial hemorrhages has not been studied specifically and needs further study.

10.8. Autoregulation in animal models of posterior circulation ischemic stroke

Matsumoto *et al* (121) used a canine model of brainstem infarction by causing permanent occlusion of perforators from the posterior cerebral arteries. Cerebral blood flow was quantified in the midbrain, thalamus and cerebral cortex by the hydrogen clearance method. The cerebral cortex maintained autoregulation and carbon dioxide reactivity in spite of induced hypotension or hypertension during the occlusion. The autoregulation of the thalamus was maintained during hypotension, but not during hypertension. However, the midbrain had markedly impaired autoregulation and carbon dioxide reactivity compared to the thalamus and cortex, which suggests a differential vulnerability to autoregulation.

The work of Shiokawa *et al* (122, 123) used bilateral carotid ligation (in spontaneously hypertensive rats) to demonstrate impaired autoregulation in the cerebrum. This had little effect on cerebellar autoregulation. However, the addition of stepwise drop in blood pressure caused an impairment of autoregulation in the cerebellum. This suggests a vulnerability to hypotension at distant areas secondary to cortical ischemia (122). This work demonstrates regional differences of cerebral blood flow in regions that are distant from the original stroke location. This effect was possibly modulated by the alpha-adrenoceptor system causing vasoconstriction secondary to cerebral hypertensive stimuli or other transtentorial signals (123).

Further rat studies of anterior circulation ischemic stroke have demonstrated impaired autoregulation secondary to ischemic stroke would depend on both the duration of occlusion and on the extent of reperfusion hyperemia (124-126). The same scenario would be expected in the posterior circulation; however this needs further study in order to be certain.

11. NEURONAL DIFFERENCES ACROSS THE TENTORIAL MEMBRANE

In humans, Drummond *et al* (127) compared median nerve somatosensory evoked potentials (MnSSEP) to both the brain stem auditory evokes responses (BAER) and cortical electroencephalogram (EEG). They used human patients under deep anesthesia with high dose sodium thiopental (STP) during staged resection of giant intracranial arteriovenous malformation (AVM). Although there were dose dependant changes in both the MnSSEP and BAER wave forms, they found that neither MnSSEP nor BAER were abolished at up to twice the dose required to produce isoelectric supratentorial EEG. These results suggest a differential neuronal response between the brainstem and cortex to an anesthetic neuronal suppression (e.g. STP).

In the anterior circulation, it has been shown that neurons have a selective vulnerability to ischemia (128) (e.g. hippocampal CA1 is more sensitive than other cerebral areas). This differential vulnerability appears to exist in the hindbrain as well. Using an established model in gerbils (129), Hata *et al* (128) occluded the bilateral extracranial vertebral arteries for 5 to 30 minutes. They assessed neuronal microtubule-associated protein 2 immunostaining, and demonstrated that the cerebellar interpositus nucleus and lateral vestibular nucleus had greatest vulnerability to ischemia, while hindbrain cardiovascular or respiratory areas were relatively resistant.

Using an in-vitro method, Donnelly *et al* (130) used sections of rat hippocampal CA1, brain stem hypoglossal (CNXII) and dorsal vagal motor nucleus (DVMN). They compared time course of hypoxia on: membrane depolarization, input resistance and extracellular potassium levels. They found different hypoxia sensitivity between the brain stem (CNXII and DVMN) and cortical (CA1) neurons, the former depolarizing faster (more excitable) and the latter depolarizing slower (less excitable). These differences were not explained by changes in the extracellular potassium concentrations. In the brain stem, the increased excitability in neurons has been associated (*in-vivo*) with functional neuronal loss (131). However, the decreased CA1 excitability may be protective and serve as an adaptive role in limiting cellular energy needs and reducing hypoxic stress ion fluxes. Authors postulated that these differences were likely due to inherent differences of the membrane properties between the brain stem and cerebral neurons, thereby leading to differential responses to oxygen deprivation.

O'Reilly *et al* (132) used intracellular electrophysiological microelectrode techniques to compare responses between hypoglossal nucleus of brain stem to the neurons in layer II/II of the temporal neocortex (NCX), during different levels of oxygen deprivation and reperfusion. They determined that cortical neurons had a much longer latency to anoxic depolarization and were more likely to recover than the hypoglossal nucleus (CNXII). They concluded that CNXII may be inherently more vulnerable to anoxic injury than cortical neurons, thereby leading to the suggested differential vulnerability.

In the reperfusion injury following a cerebral ischemic event, there is free radial production and impaired mitochondrial function (133, 134). The biochemical reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5, dipheniltetrazolium bromide (MTT) is an index of mitochondrial phosphorylation and therefore mitochondrial activity (135). Malondialdehyde (MDA) is a parameter of lipid peroxidation, and a byproduct of the breakdown of polyunsaturated fatty acids from free radical damage (136). Scorziello *et al* (137) compared the effects of oxygen and glucose deprivation (OGD) followed by reoxygenation on mitochondrial function (MTT) and lipid peroxidation (MDA) in cultured cortical and cerebellar neurons. They determined that cortical neurons were more resistant than cerebellar neurons, to free radical damage to their plasma membranes. These *in-vitro* results suggest increased vulnerability to reperfusion injury of cerebellar, compared to cerebral cells.

12. RELATIONSHIP BETWEEN SUBARACHNOID HEMORRHAGE AND THE HINDBRAIN

Using the external carotid (EC) to internal carotid (IC) ratios, Lindegaard *et al* (138) established criteria that corresponded to the angiographic evidence of vasospasm in the anterior circulation of humans and thereby determined vasospasm. Then, others (139, 140) suggested a TCD grading system of the posterior circulation based on the degree of narrowing of the vertebrobasilar arteries, and by using the ratios between basilar artery (BA) and vertebral artery (VA) size, they determined the extent of basilar artery vasospasm (BAVS). This method was useful because when it was tested in 158 patients and compared to an angiogram or CT-angiography, it yielded a sensitivity of 73-92% and specificity of 80-97% in detecting BA vasospasm (140).

Then, Sviri *et al* (141) investigated the relationship between brainstem hypoperfusion and basilar artery vasospasm (BAVS). Hypoperfusion was determined by the extent of regional brainstem blood flow by single-photon emission computed tomography (ECD-SPECT) imaging. The extent of basilar artery vasospasm was quantified by comparing baseline angiograms to angiograms of 45 patients with likely cerebral vasospasm (delayed ischemic neurological deficits) after aSAH. Half of the tested patients had delayed BAVS and/or BA narrowing of >20%. Of those with significant narrowing (>20%), 74% had BS hypoperfusion. However, BS hypoperfusion was found in 27% of patients without significant BA narrowing, suggesting the possibility of vasospasm in smaller vessels undetected the imaging. Nonetheless, the outcome at three months for the patients with BS hypoperfusion was significantly worse compared to those with unimpaired BS perfusion. These suggest significant incidence of BAVS and BS hypoperfusion in patients with severe aSAH vasospasm, which would increase their likelihood of experiencing BS ischemia.

Sviri *et al* (142) evaluated the relationship between posterior circulation hypoperfusion and basilar artery vasospasm (BAVS) after aneurysmal subarachnoid

hemorrhage (aSAH), by comparing transcranial Doppler (TCD) to multiple single-photon emission computed tomography (ECD-SPECT) imaging of both the anterior and posterior circulations during an episode of vasospasm in 162 patients. They found that 18% of patients had delayed brain stem (BS) hypoperfusion, and of those, about 80% had BAVS. Those with basilar artery vasospasm mostly experienced reduced blood flow to cerebellum (56%), occipital lobe (82%), and thalamic nuclei (68%), and 50% had high basilar artery flow velocities (>115 cm/s). According to the Glasgow clinical outcome score at 30 days, the outcome in the BAVS group (2.5) was worse than the non-BAVS group (3.3). When Sviri *et al* (143) evaluated the relationship between BAVS and patient outcome specifically, in 65 patients with severe cerebral vasospasm after aSAH, they used stepwise logistic regression for multivariate analysis, and adjusted for hydrocephalus, Hunt and Hess grading (144), Fisher grade (145), age, and aneurysmal location. They found BAVS to be a significant and independent prognostic factor for patient outcome.

To study the effects of interrupted versus uninterrupted basilar artery occlusion during basilar aneurysmal repair, Alkan *et al* (146) employed a transclival approach in rats to expose the basilar artery and place a microclip above the vertebrobasilar junction. Then, distal to the microclip placement, they performed an SAH puncture. They compared 60 minutes uninterrupted occlusion to 60 minutes interrupted, and found no difference in mortality, neurological outcome (148) or infarct area. In a follow up study, Alkan *et al* (147) found that added hypotension (60-70 mmHg MABP) led to diminished brainstem recirculation autoregulation in the interrupted occlusion group, but that a neuroprotective agent, citicoline, decreased infarct volume and mortality significantly. However, the recovery of MABP by this drug could be the reason for ameliorated autoregulation, leading to the apparent neuroprotection. Therefore, the neuroprotective mechanism of this drug in this model still remains unclear.

In lieu of increasing evidence regarding the role of posterior circulation vasospasm and/or hypoperfusion on patient outcomes after aSAH, it would be imperative that studies address this topic further. Therefore the posterior circulation needs further study in animal models, to determine the relationship between cerebral vasospasm, neurological outcome, and mortality. Although an animal model of basilar artery SAH is not new (146-150), more work needs to be done to better understand the role of the basilar circulation on the infratentorial and supratentorial pathogenesis in SAH.

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Abbreviations: 14C-IAP: 4-iodo[N-methyl-14C] antipyrine, AICA: anterior inferior cerebellar artery, BA: basilar artery, BAO: basilar artery occlusion, BAVS: basilar artery vasospasm, BS: brain stem, BAEP: brainstem auditory evoked potentials, CBF: cerebral blood flow, CT: computed tomography, IAT: intra-arterial thrombolysis, ICH: intracranial hemorrhage, IVT: intravenous thrombolysis, MABP: mean arterial blood pressure, MAP: mean arterial pressure, MAP2: microtubule associated protein, MRI: magnetic resonance imaging, PCA: posterior cerebral artery, PCHS: posterior circulation hemorrhagic stroke, PCIS: posterior circulation ischemic stroke, PComA: posterior communicating artery, PICA: posterior inferior cerebellar artery, SCA: superior cerebellar artery, SEP: somatosensory evoked potentials, SH: spontaneously hypertensive, TCD: transcranial doppler, TIA: transient ischemic attack, VA: vertebral artery, VTIA: vertebrobasilar transient ischemic attack

Key Words: Posterior-Circulation, Hindbrain, Cerebellum, Pons, Medulla, Brainstem, Vertebrobasilar, Autoregulation, Mitochondrial, Hypoperfusion, Review

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