

Review Article

Posterior Circulation Stroke: Animal Models and Mechanism of Disease

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Posterior circulation stroke refers to the vascular occlusion or bleeding, arising from the vertebrobasilar vasculature of the brain. Clinical studies show that individuals who experience posterior circulation stroke will develop significant brain injury, neurologic dysfunction, or death. Yet the therapeutic needs of this patient subpopulation remain largely unknown. Thus understanding the causative factors and the pathogenesis of brain damage is important, if posterior circulation stroke is to be prevented or treated. Appropriate animal models are necessary to achieve this understanding. This paper critically integrates the neurovascular and pathophysiological features gleaned from posterior circulation stroke animal models into clinical correlations.

1. Introduction

The posterior circulation is an understudied brain region that is affected by stroke. When translational research progresses to clinical trials, most trials will enroll very few or completely exclude posterior stroke patients [1–5]. Though posterior circulation strokes are too uncommon in many population centers to achieve sufficient numbers, other studies try to control for the heterogeneity between the anterior and posterior circulations [6, 7]. This leads to evidence-based guidelines which may not sufficiently represent some important spectrums of stroke. For these reasons, experimental animal models could be a useful tool to address emerging posterior circulation treatment strategies [8]. In this paper, we will integrate clinical features with animal models in describing characteristics of posterior circulation strokes, including the neurovascular features, and pathophysiology mechanisms founded from these experimental models.

2. Hemodynamic Posterior Circulation

The posterior circulation originates from the paired vertebral arteries and a single basilar artery, to supply the inferior thalamus, occipital lobes, midbrain, cerebellum, and brain-

stem. At the pontomedullary junction, the vertebral arteries fuse to form the basilar artery, which then courses along the ventral aspect of the pons and mesencephalon [9]. From the basilar artery, dorsolateral (circumferential) superficial vessels branch out to the lateral sides and course toward the cerebellum, while deep (paramedian) branches perforate directly into the brainstem, along the ventral aspect. The basilar artery terminates at the mesencephalic cistern, with perforator branches to parts of the diencephalon, and bifurcation into the paired posterior cerebral arteries (PCAs). The PCAs course laterally to combine with the posterior communicating arteries (PCoMAs) and then continue to supply parts of the occipital and temporal cortices. The circumferential, paramedian, and other perforator branches are called terminal vascular branches, which lack collateral flow and may potentiate focal ischemia during vertebrobasilar vessel occlusions. The pontine paramedian and the lateral cerebellar circumferential branches are the most common sites of hemorrhage. Several clinical syndromes (Table 1) are described for posterior circulation vascular injuries [10, 11].

Vascular reserve within the basilar circulation includes bidirectional flow through the AICA, PICA, and cerebellar leptomeninges [12, 13]. The leptomeningeal interconnec-

TABLE 1: Posterior circulation syndromes and associated brain region, clinical signs.

Syndrome(s)	Vessel(s)	Brain region(s)	Contralateral sign(s)	Ipsilateral sign(s)
None	VA, PICA	Cerebellum	None	Truncal, leg, and gait ataxia/dystaxia
Medial medullary, Wallenberg	ASA, VA, PICA	Caudal Medulla	Any sensory input loss hemiplegia	Horner's syndrome, tongue weakness, dysphagia, hoarseness, loss of facial sensation, nystagmus, vertigo, ataxia
Locked-in, Foville, Millard-Gubler, Marie-foix	BA, AICA	Pons	Loss of pain or temperature sensation, hemiplegia	Facial or lateral gaze weakness, dysarthria, hemiplegia, ataxia
Parinaud, Benedikt, Weber, Claude	PCA	Midbrain	Tremor, hemiplegia, motor deficit, cerebellar ataxia	Paralysis of gaze and accommodation, fixed pupils, CNIII palsy
Dejerine-Roussy	PCA	Thalamus	Pain syndrome, any sensory input loss	None
Balint, Anton	PCA	Occipital, Temporal lobes	Vision loss, blindness denial	Vision and eye movement loss, misinterpretation of visual objects, blindness denial, loss of visual-motor coordination

VA: vertebral artery; PICA: posterior inferior cerebellar artery; ASA: anterior spinal artery; BA: basilar artery; AICA: anterior inferior cerebellar artery; PCA: posterior cerebral artery; CNIII: cranial nerve three.

tions between cerebellar arteries are similar to the cerebral pial network and can reverse blood flow back through the tributaries of the basilar artery [14]. Outside the posterior circulation, the direction of blood flow can be reversed through hemodynamic connections between PComA (posterior communicating artery), first PCA segment, and carotid circulation [14]. Increased PComA vessel luminal size is directly proportional to improved patient outcome after basilar artery and first segmental PCA occlusions [15]. Patients with PComAs greater than 1 mm in diameter have less ischemic injury during carotid territory occlusions [16]. During basilar artery occlusion, PComAs reverse blood flow through the basilar bifurcation, PCA, and SCA (quadrigeminal plate) [14]. However, individual variations in arterial anatomy and the collateral circulation are common (asymmetric or single vertebral arteries, SCA and AICA branching variants, small PComAs) and these can narrow the basilar artery, diminishing vascular reserve, and leading to a greater incidence and severity of stroke [14–18].

3. Transient Posterior Brain Injury

Around ten years ago (vertebrobasilar), transient ischemic attack (TIA) was defined as follows: “a brief episode of neurologic dysfunction caused by focal brain ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction” [19]. VTIA is half the duration of carotid territory TIAs [10] and generally perceived by clinicians as having a more benign course [20–25]. Consequently, VTIA patients receive less clinical investigation and treatment [26–28]. However, a systematic review of sixteen-thousand patients found no differences between carotid and vertebrobasilar TIAs, in the rate of stroke, death, or disability [26]. In fact, VTIA is more likely to convert into full-on strokes during the acute-phase, and a third will have a stroke within 5 years [29, 30].

4. Ischemic Posterior Brain Injury

One-quarter of all ischemic strokes are located in the vertebrobasilar (VB) territory [31, 32]. These are usually caused by thrombi/emboli and rarely from vertebral artery dissection of C1-2 vertebral level trauma [10]. Patients with large vessel (basilar artery or intracranial VA) occlusions affecting the brainstem tend to have a worse prognosis while small lacunar occlusions generally do well, so long as cardiorespiratory centers are intact ([6]; clinical features are summarized in Table 1).

Patient outcomes after VB ischemic stroke have been somewhat the subject of debate. The Oxfordshire Community Stroke Project [31] prospectively followed 129 patients and found a 14% mortality and 18% major disability rate, while the New England Medical Centre Posterior Circulation Registry (NEMC-PCR) [33] found a 4% (death) and 18% (disability) rate, with a prospective study of 407 patients. For basilar artery occlusion (BAO), the most severe form of VB ischemic stroke, a systematic analysis of 10 published case series and 344 patients, reported an overall death or dependency rate of 76% [34], while the NEMC-PCR study with 87 patients reported poor outcomes in 28–58% of patients [35].

5. Hemorrhagic Posterior Brain Injury

One-fifth of all intracerebral hemorrhage (ICH) occurs in the cerebellum or brainstem [36, 37]. Brainstem hemorrhages have a 65% mortality rate and around 40% after cerebellar hemorrhage [38–40]. Prolonged endovascular cerebrovascular damage from uncontrolled hypertension leads to arteriosclerotic and amyloid angiopathic changes, vessel fragility, and rupture at the deep cerebellar vessels or brainstem basilar (paramedian) branches [37, 41]. Less common relations to occurrence are cancer, coagulopathy, or vascular anomalies (arterial-venous malformations, aneurysms,

cavernomas, and dural arteriovenous fistulas) [37, 41]. For most patients, supportive care is the only treatment rendered, since surgery is only available for one-quarter of hospitalized cerebellar hemorrhage patients, and the brainstem is not surgically accessible [42–45]. Mechanisms of infratentorial hemorrhage have never been studied and to this end we have developed animal models using collagenase to address this brain hemorrhage subpopulation [46, 47].

6. Animal Studies

Experimental models are available to study ischemic posterior circulation stroke [48]. Many animal studies of anterior circulation ischemic stroke have demonstrated impaired autoregulation after ischemic stroke. The extent of which would depend on occlusion duration and extent of reperfusion hyperemia [49–51]. These mechanisms warrant further study—this can be achieved using available animal models of posterior circulation stroke. Under experimental conditions, the standardized progressive hypotension in rats showed that autoregulatory kinetics remained intact at the cerebrum, while a progressive loss of autoregulatory efficacy in the cerebellum [52]. As a next step, however, changes in mean arterial blood pressure (MABP) and CO₂ levels (in cats) while measuring blood flow (hydrogen clearance method) in the cerebrum, cerebellum, and spinal cord found greater susceptibility to pressure-dependant ischemia in the cerebrum and spinal cord than cerebellum, which was relatively resistant [53].

Corroborative studies [54] used transcranial Doppler methods for comparing blood flow in supratentorial and infratentorial brain compartments during increasing intracranial pressures, in the rabbit experimental model. Essentially, the maximum vasomotor activity amplitude of occurred 30 seconds later in the basilar artery, compared with the carotids. Such reports demonstrate that delays are present in the effect of intracranial pressure upon hindbrain microvascular tone. Using a canine experimental model of permanent occlusion to posterior cerebral artery perforators [55] with the ability to monitor cerebral blood flow (autoregulation) and carbon dioxide reactivity, in response to induced hypotension/hypertension, it was found that cerebral cortex maintained autoregulation and carbon dioxide reactivity, while thalamic autoregulation was maintained in hypotension, but not during episodic hypertension. On the other hand, the midbrain retained marked impaired autoregulation and carbon dioxide reactivity. Such findings reveal differential brain vulnerability following permanent vascular occlusions. In essence, animal studies indicate that brainstem nuclei decompensated compared to forebrain regions, despite abundant amounts of posterior collateral circulation.

The animal model of bilateral carotid ligation using spontaneously hypertensive rats showed impaired autoregulation in the cerebrum [56]. However, the addition of stepwise drops in mean arterial pressures caused impairment of cerebellar autoregulation as well. Hypothetically, it is possible that vulnerability to hypotension in areas distant

from the stroke ictus is modulated by alpha-adrenoceptor (vasoconstrictive) neurons responding to cerebral (transtentorial) hypertension signals [57]. The collateral vascular compensation may be a function of age, since bilateral carotid occlusion causes greater dependence upon basilar flow in adult rats, compared to dependence upon extracerebral midline collaterals in younger experimental animals [58].

7. Animal Models: Vascular Responses to Stroke

Experimental studies reveal that similar cerebrovascular mechanisms are found after ischemic and hemorrhagic stroke [59]. Normally, cerebrovascular autoregulation maintains optimal brain tissue perfusion through arterial constriction/dilation in response to local levels of CO₂ and systemic variations of blood pressures (MABP) [60]. Human stroke leads to damaged cerebral autoregulation capacity and greater dependence upon systemic arterial pressure [61–63] occurring after both carotid and vertebrobasilar-based vascular territories [62, 64]. This impairment is recognized as an important mechanism of secondary brain injury and edema formation, following human ischemic stroke [65] and intracerebral hemorrhage [66]. There is a rationale behind the tight hemodynamic and respiratory control in the intensive care units.

Animal studies show that the vertebrobasilar vessels have a greater capacity to mechanically vasodilate and vasoconstrict compared to carotid-based vasculature, suggesting greater dynamic autoregulatory ability [67–69]. This may be a mechanism enabling the hindbrain to divert blood flow to the carotid system during cerebrovascular strain, since drops in total brain perfusion lead to proportionally greater diminished flow across the basilar compared to the middle-cerebral artery [70]. When systemic CO₂ and blood pressure changes are superimposed upon permanent posterior cerebral artery occlusion, in dogs, this showed graded autoregulatory decompensation caudally from the supratentorial region to the brainstem, while carotid-based autoregulation was preserved [55]. Experiments in rats show cerebral sparing, while systemic hypotension causes progressive decline in cerebellar autoregulatory kinetics, and carotid autoregulatory kinetics remain intact [52]. The impairment of cerebellar autoregulation also occurs after bilateral carotid ligation in spontaneously hypertensive rats [57]. Conversely, the combination of hypocapnia with systemic hypotension, in cats, caused greater ischemic susceptibility in cortical brain-regions compared with the cerebellum [53]. Cerebellar autoregulatory kinetics may, therefore, accommodate CO₂ fluctuation more favorably, in the face of hypoperfusion, while drops in arterial pressures, without systemic CO₂ change, would affect the cerebellum more severely [52].

In most species, the cerebellum and brainstem have an abundance of white matter tracts. Magnetic resonance imaging (MRI) perfusion and diffusion studies in humans have determined white matter to have an infarction threshold of 20 mL/100 g/minute, while gray matter can sustain flow down to infarctions starting at 12 mL/100 g/minute [71].

A greater density of white matter tracts in the hindbrain would imply greater vulnerability to ischemic injury. Therefore the viability of brainstem cardiorespiratory centers during periods of severe systemic hypotension, global cerebral ischemia, and cardiac arrest will necessitate further study.

8. Animal Models: Neural Consequences from Stroke

Animal models show that ischemic interruption of cerebral blood flow leads to hypoxic and anoxic brain injury, increased neuronal excitability, and cell death [72]. Reperfusion injury further augments this damage through free radical production and mitochondrial dysfunction [73, 74] and similar mechanisms are at play after hemorrhagic stroke also [59]. Neurons in the CA1 hippocampal region are particularly vulnerable to ischemia; yet, experimentally, these cells are more resistant to damage than several areas of the hindbrain [75, 76]. Electrophysiological studies after hypoxic injury have shown greater neuronal excitability in the hypoglossal (CNXII) and dorsal vagal motor (DVMN) cranial nuclei of the brainstem compared to hippocampal CA1 regions [76]. Animal models show that anoxia of the hypoglossal nucleus will have both greater initial injury and impaired recovery compared with these temporal lobe neurons [77]. In vitro simulation of ischemic reperfusion injury, using cell cultures of oxygen-glucose deprivation followed by reoxygenation (OGD-R), showed greater free-radical injury (lipid peroxidation) and mitochondrial impairment in cerebellar cells compared to cerebral cortical cell culture [78]. Experiments comparing cerebellum with brainstem injury, after vertebral arterial occlusions in gerbils, showed greatest amount of cell death near regions controlling coordination and balance (cerebellar interpositus and lateral vestibular nuclei), while brainstem cardiorespiratory areas remain relatively more intact [75]. The scattered mosaic nature of brainstem nuclei means that this is not simply a redistribution of blood flow and is likely a feature of the neuronal environment, and this deserves further study.

Experimental studies reveal significant cerebellar fastigial nuclei (FN) involvement in the regulation of blood pressure and flow [79–81]. This occurs via integration of autonomic signals from vestibular and cerebellar Purkinje neurons [82, 83]. FN also modulate the function of adjacent medullary structures and autonomic spinal intermediolateral column neurons [84, 85]. In primates, these nuclei interconnect with vestibular (lateral and inferior), reticular (lateral, paramedian, and gigantocellular), and cervical spinal anterior gray neurons [86]. Animal models demonstrate that electrical stimulation of the FN leads to pressor responses with tachycardia, as mediated by fibers passing through, or very close to, the FN, while chemical activation causes a depressor response, with bradycardia via intrinsic FN neuronal activity [87–89]. Taken together, cerebellar fastigial nuclei serve important cardiovascular functions, the manner of which is of significant clinical interest, since cerebellar injury in association with cardiopulmonary consequences is a common occurrence [90–93].

Neurons of the area postrema (AP) also contribute to cardiovascular regulation [94–97]. Biochemically, the cell-surface receptors of circulating molecules: angiotensin II (AT1), and vasopressin (V1), are expressed within this brain region [98–100]. Here, the angiotensin II neurohormone can reset the baroreflex to higher blood pressure levels through indirect interactions with the nucleus of the solitary tract and interconnections within the medulla [101–103]. These nuclei can also modulate the cardiovascular regulatory effects of other neuropeptides—such as vasopressin. While this homeostatic effector readily binds somatic V2 type receptors, causing peripheral vasoconstriction, V1 receptor binding-interactions within the area postrema will paradoxically enhance baroreflex sensitivity towards activation at lower threshold pressure set-points [104–106]. All together, these pathways help keep the balance of complex cerebrovascular systems.

9. Development and Gender

Young children exhibit sex differences in the autoregulatory capacity between anterior and posterior circulations. Female children, ages 4–8 years, have higher flow velocities for both the middle cerebral and basilar arteries, while both sexes exhibit greater flow velocity in the middle cerebral compared to basilar arteries [107]. Later, autoregulatory capacities begin to emerge with females (10–16 years old) having greater capacity in the basilar artery than males, but males having the advantage of greater MCA autoregulatory index [108]. Up through adolescence, however, females continue to have higher flow velocities (compared to males) for both the middle cerebral and basilar arteries. This may indicate a gender-specific ability to handle an occlusive thrombus in the hindbrain. Further studies are needed to understand these gender differences.

10. Conclusion

The hindbrain injury pathogenesis, prevention, and treatment remain largely unknown, and animal models may be necessary to achieve this understanding. Furthermore, injury to this area can be particularly devastating. This brain region may have less innate neurovascular protective mechanisms and greater amount of cell death and injury in comparison to supratentorial strokes. Significant experimental study has been done for posterior circulation stroke. Future studies can choose from an array of animal models, to test interventions for reversing the mechanisms of injury in this brain region. The strength of this paper is related to the comprehensive nature of the information presented. In limitation, future reports will need to further critically appraise the reported data in the context of available evidence.

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