Review

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Review

From Artery to Memory: A Comparative Review of Vascular Cognitive Impairment Surgical Models

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Abstract

Vascular cognitive impairment (VCI) is a broad umbrella term encompassing a spectrum of cerebrovascular diseases ranging from mild clinical cognitive impairment to advanced vascular dementia. It represents the second most prevalent etiology of dementia among older adults, following Alzheimer's disease (AD). VCI, however, frequently coincides with AD, synergistically contributing to neurodegeneration, reductions in white matter (WM) volume, and progressive cognitive dysfunction. While the precise pathophysiology of VCI remains largely unknown, several animal models have been utilized to better understand the underlying mechanisms of the disease and develop targeted prevention and therapeutic strategies. Reproducible rodent models of common carotid artery occlusion or stenosis capture essential features of human VCI and provide a framework to examine how both transient and chronic cerebral hypoperfusion (CCH) contribute to neurodegenerative pathways and VCI-related pathologies through alterations in neural metabolism, neurotransmitter regulation, cerebral tissue damage and, ultimately, memory function. However, broad translational gaps remain between gyrencephalic humans and lissencephalic rodents, as their differing cerebrovascular architecture does not fully recapitulate the pathogenesis or clinical symptoms of VCI or vascular dementia, as a subset. As such, the objective of this review is to highlight the principal methodologies of existing VCI animal models, with particular emphasis on histological and functional consequences of CCH, while evaluating their strengths, limitations, and clinical relevance to human disease.

Keywords: vascular cognitive impairment; neurogenerative disease; cerebral hypoperfusion; cognitive decline; white matter; common carotid artery; surgical models

1. Introduction

Vascular cognitive impairment (VCI) is a chronic and degenerative cerebrovascular disease characterized by white matter (WM) lesions and degeneration, microinfarcts, small vessel disease, and progressive cognitive dysfunction [1]. VCI encompasses a broad spectrum of cerebrovascular disease, from mild cognitive dysfunction to clinically diagnosed Alzheimer's Disease (AD) and vascular dementia. The World Health Organization broadly identifies dementia as the 7th leading cause of death globally, with 57 million affected individuals in 2021 and an expected annual increase by 10 million [2]. While the most prevalent form of dementia is AD, contributing to 60-70% of cases, VCI has more recently been identified as both an independent form of dementia and, perhaps more significantly, a concomitant contributor to mixed dementia [2]. A growing body of literature increasingly supports a mixed pathological mechanism of VCI and AD, with primary overlapping

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outcomes including cerebral amyloid angiopathy, small vessel disease, and diffuse WM changes which synergistically drive disease onset and progression [1,3].

There are numerous reviews available which thoroughly analyze the complex pathophysiology underlying the clinical symptoms of VCI, and more specifically, vascular dementia [4–8]. Vascular dementia, as the most severe end-stage form of VCI, is included in this review due to its higher prevalence in clinical literature and its close alignment with the severity of histological and functional outcomes reported in surgical animal VCI models. To highlight the key points most commonly underscored in existing VCI surgical animal model literature, this review will focus on histological changes, neurotransmitter and neurometabolic dysregulation, memory and cognition deficits, and global cerebral perfusion changes. The interaction of cerebral blood flow (CBF) and neural cells is tightly controlled by the neurovascular unit, a network of interactive neurons, astrocytes, and microglia [4]. As CBF decreases in the pathologic brain, the nutrient supply is decreased, intercellular signaling is impeded, debris clearance mechanisms are inhibited, and overall cell dysregulation and death becomes prominent. Concomitantly with such cellular changes, neurotransmitter and neurometabolic homeostasis is interrupted in the VCI brain. Alterations in various neurotransmitters have been linked to clinical symptoms associated with VCI and vascular dementia such as cognitive decline secondary to cholinergic and glutamatergic deficits, EEG brainwave pattern changes associated with excitatory and inhibitory changes, and psychiatric symptoms related to monoamine neurotransmission modifications [9]. By exploring the currently used models of cerebral hypoperfusion and their respective effects on the aforementioned pathologies, this review will establish optimal conditions under which transient or chronic ischemia may be most effectively utilized to recapitulate human disease. Further, this knowledge may be leveraged for the development of novel biomarkers, diagnostic tools, and therapies targeting VCI prevention and treatment strategies.

The synchronicity of numerous pathologies associated with cognitive decline has challenged the development and implementation of comprehensive diagnostics or effective therapeutics within clinical practice [1,10]. In efforts to overcome this challenge, various animal models have been developed to study VCI and pinpoint biomarkers, disease stages, and therapeutic targets. Transient VCI models involve the temporary occlusion of both common carotid arteries (2-VO), or the temporary occlusion of both carotid arteries simultaneously with the permanent occlusion of both vertebral arteries (4-VO) with subsequent reperfusion [11–21]. These models offer insight into both hypoperfusion and reperfusion injuries but are limited by missing key components of human disease that are actuated by chronic hypoperfusion. Chronic global ischemia induction is achieved through permanent ligation of both common carotid arteries in rats and mice (BCCAO), but disproportionate mortality rates in mouse BCCAO models necessitated an alternative approach. BCCAO effectively produces chronic cerebral hypoperfusion (CCH), WM lesions, gliosis, blood-brain barrier (BBB) disruption, and cognitive deficits in rats, but not mice. Mouse VCI models have achieved CCH by narrowing the vessel lumen rather than occluding it, twining a specialized micro-coil around one or both common carotid arteries. Bilateral stenosis of the common carotids (BCAS) in this method yields equivocal pathological and functional outcomes with amended survival rates [22,23]. Most recently, surgical VCI models gradually occlude common carotid artery luminal diameter using ameroid constrictors, achieving chronic cerebral hypoperfusion without acute severe ischemic injury. These gradual occlusion VCI models have effectively reproduced key pathophysiological features of clinical VCI, such as impaired CBF, development of WM lesions, increased neuronal inflammation, BBB disruption, and working memory deficits without extraneous pathologies that more closely align with stroke or acute traumatic injury. Achieving a CCH state through occlusion or stenosis of the common carotid arteries has become a reliable model for evaluating consequent brain ischemia pathologies. Modern VCI surgical models clearly demonstrate drastic and persistent reductions in CBF, disrupted glucose metabolism, neurotransmitter imbalance, and neurodegeneration which align with clinical VCI pathophysiology, allowing researchers to utilize these models to pursue novel diagnostic and therapeutic measures.

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While numerous models surgically induce global transient or CCH in rodents, other non-surgical methods and large animal hypoperfusion models have been used with unique limitations. Common non-surgical models include dietary manipulation to induce hyperhomocysteinemia, cerebral amyloid angiopathy induction, genetic manipulation to trigger cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) pathology, and replication of post-stroke vasculopathy via stroke prone spontaneously hypertensive rats [24–27]. Surgically induced VCI models most successfully recapitulate the heterogeneity of physiological and cognitive outcomes consequential to CCH with greater replicability and predictability than the non-surgical methods [3,25,26]. Rodent VCI models are the most prevalent, with limited literature available utilizing large animal models due to financial, practical, and ethical constraints [27,28]. Ovine and caprine models of middle cerebral artery occlusion most closely replicate ischemic stroke pathology [29,30]. Non-human primate models offer greater translatability of cognitive and neuroimaging outcomes, but due to the complexity of surgical induction techniques, most models evaluate non-surgical dementia comorbidities [27,31]. Further investigations are warranted in large animal models to improve the translatability of research outcomes from VCI modeling.

This review will emphasize the utility and clinical relevance of surgical VCI models, discussing occlusive, stenotic, or gradual occlusive models of the common carotid and/or vertebral arteries. Within various types of surgical models, histological and immunohistochemical changes following VCI induction will be evaluated. When applicable, clinically relevant advanced imaging data will be integrated to assess the development and progression of cerebral tissue degeneration in relationship with cognitive and neurological deficits across both acute and chronic timepoints. These findings from animal models will be compared to patient outcomes to highlight principal strengths and notable limitations of the currently utilized VCI animal models while emphasizing the necessity for both existing model optimization and the continued development of novel models.

1.2. Search Strategy and Selection Criteria

The literature selected for this review was obtained via PubMed, Google Scholar, ScienceDirect, Springer, Frontiers, and Nature. The search was limited to articles published between 1979 and 2025. The following keywords were used to identify and refine relevant articles: vascular cognitive impairment, VCI, neurovascular unit, neurotransmitter, neuroenergetic, neurometabolic, animal models, surgical models, common carotid artery ligation surgery common carotid artery stenosis surgery, gradual occlusion common carotid surgery, chronic cerebral hypoperfusion, vascular dementia, neurodegenerative disease, cognitive impairment, common carotid occlusion, common carotid stenosis, BCCAO, BCAS, 2-VO, 4-VO, transient occlusion, ameroid constrictor, ameroid ring, casein constrictor, magnetic resonance arteriography, magnetic resonance imaging, pig, porcine, swine, sheep, ovine, goat, caprine, non-human primate, large animal model, mouse, murine, rat, rodent small animal model.

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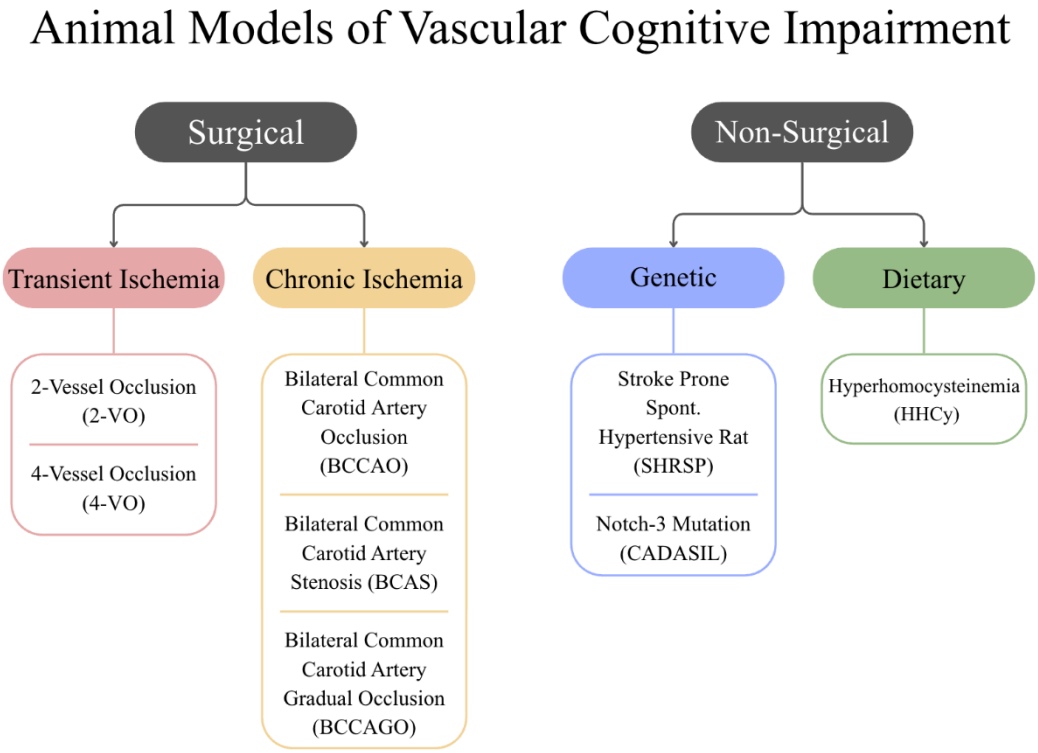

Figure 1. Classification of surgical and non-surgical vascular cognitive impairment (VCI) animal models. VCI surgical models can be considered transient or chronic, where the former causes brief vascular injury and the latter produces progressive or sustained reductions in cerebral blood flow (CBF). Transient global ischemia models include temporary two-vessel occlusion (2-VO) and four-vessel occlusion (4-VO) models. Chronic global ischemia models include bilateral common carotid artery occlusion (BCCAO), bilateral common carotid artery stenosis (BCAS), and bilateral common carotid artery gradual occlusion (BCCAGO). Non-surgical models utilize genetic manipulation which includes selective breeding for the stroke prone spontaneously hypertensive rat and knockout Notch-3 mutations to induce cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy as well as the dietary induction of hyperhomocysteinemia.

2. Vascular Cognitive Impairment Surgical Animal Models

2.1. Transient Global Ischemia

2.1.1. Two-Vessel Occlusion with Reperfusion (2-VO)

The two-vessel occlusion (2-VO) rat model is one of the earliest VCI surgical animal models in which transient global cerebral hypoperfusion is achieved through temporary restriction of blood flow bilaterally through the common carotid arteries. The common carotid arteries are identified and isolated from the surrounding cervical tissue through a ventral incision. Metal atraumatic arterial clamps are placed around both carotid arteries and occlusion is maintained for 8-60 minute intervals that may be repeated [13,32,33]. Reperfusion is permitted to occur from 1 hour to 7 days after removal of ligation clips prior to sacrifice [13–15,32–35].

This model is procedurally similar to Longa's ischemic stroke rodent model, in which the common carotid artery is transiently occluded and the external carotid artery ligated [36–39]. The transient occlusion of the common carotid arteries in 2-VO and the external carotids in an ischemic stroke model both produce drastic reductions in global CBF [40,41]. During the 2-VO occlusive phase, CBF was reduced to 11.2±1.1% of baseline (i.e., pre-operative) flow [33,40,41]. Immediately following ligation clip removal, CBF was restored to 44.9±6.3% of baseline [33]. In comparison, CBF decreased to 17.9±5.0% immediately following ischemic stroke modeling and remained comparably depressed, at or below 50% baseline at 30-120 minutes post-ischemia [38,42]. Interestingly, CBF specifically

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within cortical branches was generally restored by 120 minutes of post-stroke reperfusion, but striatal CBF typically remained depressed [43,44]. 2-VO models have demonstrated preferential CBF reductions in the hippocampus and striatum which correlate most robustly with neuroenergetic alteration and WM lesioning [14]. Based upon CBF levels, it is apparent that modeling VCI using a 2-VO method precariously overlaps with ischemic stroke modeling which should be considered in future studies.

Histologically, 2-VO induces several deficits across neural cell types through pro-inflammatory mediators and enzymatic dysregulation. Pyramidal CA1 neuron populations decreased by up to 50% globally following 2-VO with reperfusion [13,20,41]. By 3 days post-operatively, a significant portion of CA1 neurons were morphologically abnormal or displayed pyknotic nuclei [20]. Viable and metabolically active neural cell populations were reduced in both the striatum and cortex acutely (1 day) after 2-VO. However, reductions in hippocampal neurons did not appear with equal severity until later timepoints (7 days), indicating that apoptosis and degeneration of cerebral tissue is both compartment and time specific following ischemia and reperfusion with the 2-VO method [32].

Microglia play a complex, dual-purpose role in the pathogenesis of VCI, where they act acutely to mitigate damage from ischemic injury, but chronically contribute to numerous degenerative processes mediated by prolonged neuroinflammation. In the 2-VO model, mild microglial activation occurred immediately following reperfusion in groups with a 10 and 15 minute ischemic interval; whereas 20-minute occlusion models exhibited robust microglial activation less than 1 hour post-reperfusion [34]. Extended periods (up to 72 hours) after 2-VO, microglial upregulation regressed to categorically mild and moderate intensities; however, intense Iba-1+ populations did persist at 3 and 7 days following transient ischemia [33,34]. Immediate post-operative microglial upregulation indicates an urgent neuroinflammatory response to acute ischemic injury, which is expected given the glia's role in pro-inflammatory injury mitigation. While the acute microglial response is vital for survival and recovery, chronic activation and neuroinflammation contributes to the cyclical degradation of healthy neural tissue and resultant neurodegenerative disease [45,46]. Observed ramified morphological shifts suggest a more chronic microglial involvement in deleterious phagocytosis and synaptic pruning following ischemic injury [47]. This chronic reperfusion injury phase mediated by neuroinflammation represents a prime target for potential therapies, where a reversible amount of microglial activation could be controlled to reduce inflammation and subsequent tissue damage; however, the 2-VO model limitations constrain its utility to that goal.

During acute neural inflammation, mixed metalloproteinases (MMPs) are abundant and play a pivotal role in endothelial tight junction cleavage and subsequent BBB breakdown. The synchronous perpetuation of these MMPs (namely, MMP-2 and MMP-9) contributes to eventual BBB disruption in VCI pathophysiology, yet the brevity of 2-VO studies limits evaluation of BBB integrity at chronic timepoints following restitution of blood flow [48]. MMP-2 is largely responsible for the enzymatic degradation of myelin-basic protein (MBP) and endothelial tight junction proteins. When persistently upregulated, the mechanistic action of MMP-2 detrimentally contributes to demyelination and BBB disruption, allowing larger reactive oxygen species (ROS) and pro-inflammatory cytokines to degrade cerebral tissue [33,49,50]. Lakhan et al. asserts that MMP-9 is more closely associated with direct BBB degradation through cleavage of both tight junction proteins and basal membrane proteins [51]. Studies show that up to 7 days following reperfusion in a 2-VO model, MMP-2 was significantly elevated despite insignificant changes in MMP-9, suggesting that increased WM damage at these timepoints may be due to enzymatic activity of MMP-2 rather than active BBB damage through MMP-9 endothelial damage [33,51]. However, it has been shown that MMPs are involved in the degradation of MBP, thus contributing to demyelination and WM lesion formation [33]. MMP-mediated neural disruption may be studied using the 2-VO model; however, additional contributors to BBB breakdown and myelin damage must be considered within the short post-reperfusion time course.

The 2-VO model only mimics the chronic ischemic conditions of VCI acutely, limiting its utility for longitudinal changes in WM following CCH; however, studies have shown that WM damage is still detectable. Specifically, viable oligodendrocyte loss is implicated in both de- and dysmyelination.

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Oligodendrocyte populations were reduced in WM tracts at both 3 and 7 days post 2-VO, the loss of which contributed directly to downstream axonal and synaptic damage [33]. While precise mechanisms remain challenging to ascertain, ischemic-induced oligodendrocyte apoptosis may play a critical role in the delayed development of chronic inflammation and WM injury [33]. In addition to direct oligodendrocyte loss, astrocytosis was notably increased in GFAP+ hypoxic WM at 1-7 days post-procedure [33]. This hypertrophic astrocyte response following ischemic and reperfusion injury has been shown to contribute to myelin debris accumulation and inhibition of myelin homeostatic pathways (LCN2/LRP1) [52]. Given the acute sacrifice timepoints (up to 7 days) of 2-VO models, chronic WM damage in response to proliferative neuroinflammation is difficult to determine.

Imbalances in neurotransmitter release secondary to acute ischemia (such as dopamine, GABA, and glutamate) may delineate a relationship between ischemic-induced excitotoxicity, neuronal apoptotic cascades, oligodendrocyte and myelin loss, and functional memory regression [14,53]. Glutamate, specifically, contributes to cyclical excitotoxity in conjunction with an imbalanced inward cellular flow of calcium [54]. Excessive circulating glutamate overstimulates NMDA receptors, triggering apoptotic neuronal cell death pathways, contributing to downstream neuronal density reductions in both 2-VO VCI models and ischemic stroke models [16,54–56]. Furthermore, Wahul et al. reported decreased expression of CA1 and CA2 hippocampal NMDA receptors, suggesting a mechanism underlying long-term memory deficits in the 2VO VCI model [32]. Acute neuronal cell death contributes to subsequent cognitive decline. Accordingly, the 2-VO model may prove particularly useful for investigating neurotransmitter-based therapeutic targets in post-stroke dementia due to the linear relationship between acute neurotransmitter imbalance following ischemic stroke and chronic cognitive decline [54].

Heim et al. suggests a positive correlation between extracellular neurotransmitter concentration differences and progressive cognitive deficiency in a 2-VO rat model [14]. Robust discrepancies in Morris water maze performance indicated spatial working and reference memory impairment by 7 days following a 10 minute 2-VO ischemic injury in rats [13,14,32]. Latency to escape increased consistently from 6-13 months post-operatively, indicating regression of learning and motor skills [14]. Additionally, 2-VO rats exhibited worsened outcomes of the 8-arm radial maze than sham animals, taking more days to attain satisfactory training acquisition criterion and committing more errors during testing [13]. Discrepancies in the 8-arm radial maze correlate 2-VO with impaired spatial working memory and spatial learning. The correlation between spatial memory deficits and histological changes do recapitulate some VCI patient outcomes, particularly acute histological changes and subsequent cognitive deficiencies [33,38,42].

2-VO Model Considerations

Transient ischemia models permitting reperfusion may provide greater insight into post-stroke or transient ischemic attack pathology rather than mild to moderate VCI, uniquely characterized by chronic and progressive disease mechanisms with limited recovery. Sequential removal of atraumatic arterial clamps reduces the risk of reperfusion injury, a phenomenon more characteristic of acute ischemic stroke than VCI, but still relevant to chronic post-stroke dementia pathophysiology. The possibility of reperfusion injury in the 2-VO model may be of interest for cohorts surviving greater than 7 days, as oxidative stress, neuroinflammation, and microvascular obstruction may inform prolonged outcomes [57]. An adaptation of the 2-VO model to greater than 6-month survivability may better inform specific post-stroke cognitive impairment [58,59]. While the 2-VO model acutely and severely reduces CBF, cerebral tissue does not experience the sustained hypoxia that generates VCI-associated neurometabolic deficits [60–62]. Transient hypoperfusion models do successfully recapitulate a multitude of acute post-ischemic outcomes, such as diffuse WM lesions, neuroinflammation, gliosis, neuronal loss, and cognitive deficits. These models, however, only evaluate acute timepoints, which do not accurately reflect the progressively degenerative nature of VCI. Additionally, the transient ischemic injury due to reperfusion poorly replicates the gradual deterioration of cerebral small vessels that underlies the majority of mixed-pathology dementia [63].

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Although 2 VO is widely used in both VCI and ischemic stroke research, successfully modeling several aspects of human pathophysiology, its limitations must be acknowledged to guide future studies.

2.1.2. Four-Vessel Occlusion with Reperfusion (4-VO)

The four-vessel occlusion (4-VO) model reduces CBF greatly and produces severe secondary hypoxia. This model was first described by Pulsinelli and Brierly in 1979 with the goal of creating a model to override the rat's well-adapted Circle of Willis [18]. In 4-VO transient global ischemia models, both common carotid arteries are isolated through a ventral midline incision and are surgically clamped for 5-20 minutes using specialized atraumatic arterial clamps or hydraulic pressure occluders [11,16–18]. A second incision behind the occipital bone allows access to the bilateral vertebral arteries, which are permanently occluded [11,15,17,18,21]. Different from the 2-VO model, 4-VO results in a mixed model of permanent and transient occlusion with reperfusion. The 4-VO model indicates that histological changes and a marked reduction in cognitive integrity are relative to ischemic duration, highlighting a vital relationship between cerebral hypoperfusion and cognitive impairment via cell death [15,21,64–66]. These findings may be attributed to the occlusion of posterior vessels (i.e., the vertebral arteries) in addition to the forebrain ischemia which immediately and drastically reduces CBF to 12-14% of baseline during occlusion [67]. Schmidt-Kaster et al., for example, evaluated regional CBF across numerous cerebral structures, noting reductions as severe as 2% of sham values in regions of the striatum and 6% of sham in the dorsal hippocampus when measured at 29 minutes [19].

Similarly to 2-VO, 4-VO causes rapid and detrimental histological outcomes. 4-VO generates acute CA1 hippocampal neuronal apoptosis with WM degradation following 10-minute transient common carotid occlusion and vertebral artery cauterization [11,17,68]. Neuronal survivability is negatively correlated with both the duration of vessel occlusion and the frequency of intermittent transient occlusion intervals [21,65]. A single 10-minute ischemic interval produced no significant CA1 neuronal density reduction at 24 hours post-reperfusion and a 45% reduction at 7 days. CA1 hippocampal neurons were reduced, however, by 75 and 79% when undergoing two and three 10-minute ischemic intervals, respectively [21]. In a later study by Song et al., CA1 hippocampal neuronal density declined to 106.4±9.4 cells/mm2 as compared to 335.8±10.0 cells/mm2 in the sham group, or approximately a 31% decrease in cell density [68]. Proportionally to the greater degree of ischemia, 4-VO reduces viable hippocampal neurons more drastically than is reported in both 2-VO and clinical dementia pathology. Acutely following reperfusion, the 2-VO model demonstrated insignificant hippocampal neuron loss; however, a 40% neuron loss was significant in the CA1, CA3, and dentate gyrus regions of the hippocampus in the 4-VO model [32]. CA1 neuron loss is correlated with poor composite memory scores (r=0.62) in clinical dementia data where CA1 neuron populations are reduced by 48% as compared to non-Alzheimer's patients [69]. The increased ischemic severity in the 4-VO, as compared to the 2-VO model, proportionally increases neuronal damage and, importantly, drives neuronal loss to clinical levels, which may indicate the value of 4-VO as a model to study the specific consequences of neuronal loss in relationship with dementia symptoms.

As a primary protective cell for neurons, oligodendrocytes are also highly sensitive to ischemia, dying rapidly in the cortex and thalamus following ischemic injury [17,33,70,71]. Healthy oligodendrocyte population reductions may contribute to secondary demyelination, resulting in poor synaptic integrity and progressive cognitive decline, as is observed in clinical vascular dementia pathology [72–74]. Oligodendrocytes were both reduced in number and morphologically abnormal by 48 hours of reperfusion in ischemic stroke rodent models, consistent with 4-VO patterning [75]. Increased MMP-2 and MMP-9 activity following both transient 2-VO and 4-VO ischemia suggests an important relationship between enzymatic BBB degradation and oligodendrocyte-associated demyelination that may be informative in the development of therapeutic targets [33,76,77]. The adaptation of oligodendrocyte-targeting therapeutics in a 4-VO model of ischemia may offer insight

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into degenerative disease prevention following acute ischemic events such as cerebral infarction or multi-stroke dementia.

Abnormal neurometabolism is commonly identified in neurodegenerative diseases like AD and VCI, and 4-VO ischemic injury recapitulates this disease. Schmidt-Kastner et al. reported increased free glucose concentrations in all evaluated brain areas at all circulation timepoints, indicating decreased glucose uptake or impaired metabolic activity as a consequence of hypoperfusion [19]. The authors found a near complete loss of ATP bioluminescence in the rodent forebrain acutely, with striatal ATP levels diminishing 24 hours after reperfusion [19]. Glucose metabolites not only support ATP production as the primary energy source for the brain, but they also modulate various functions of neurons and glial cells. In 4-VO models, ATP depletion and glucose metabolite dysregulation can result in microglia activation, ROS production, and mitochondrial dysfunction which all contribute to dementia-like pathophysiology [78].

In addition to neurometabolism dysfunction, neurotransmitter concentration is significantly reduced after reperfusion in 4-VO models, indicative of excitotoxic synaptic damage and compromised neuronal signaling [16]. In a study by Chung et al., acetylcholine activity was transiently increased during ischemia, but remained significantly decreased after 7 days, specifically in the frontal cortex and dorsal hippocampus [21]. Conversely, dorsal hippocampus glutamate concentrations reached significant elevation by 7 days post-reperfusion, indicating metabolic imbalance with impaired reuptake [16]. Acetylcholine concentrations in cerebrospinal fluid are significantly lower in multiple-infarct dementia patients versus healthy controls, which was positively correlated with worse dementia scale scores [79]. Evaluation of metabolite concentrations may serve as an early VCI marker, and the restitution of normal neurometabolism may offer a possible therapeutic target for future studies to evaluate [79]. 4-VO induced neurotransmitter dysfunction exhibits similar patterns to 2-VO, supporting a pertinent role of neurotransmitter dysregulation in the development of working memory impairment seen in both models [16,54,55].

Spatial working memory impairment, evaluated via the 8-arm radial maze, increased with ischemic duration following repeated occlusions under anesthesia, with deficits emerging early (within 24 hours) and persisting 7 days following surgery. [21]. Rats undergoing 10-, and 20-minute ischemic intervals, but not 5-minute, exhibited a decrease in spatial cognition performance, without any significant difficulty in mobility, indicating diminished memory and cognitive skills induced by CCH dependent upon time under ischemia [16]. As such, the degree of cognitive impairment appears proportional to the repetition of or total time under ischemia, with rats undergoing two 10-minute occlusion intervals exhibiting greater reductions in 8-arm radial maze performance than rats subjected to one 10-minute occlusion interval [15,67]. Repetitive ischemic injuries resulting in cognitive deficits do modulate aspects of multi-infarct dementia, in which patients exhibit lowered working memory abilities and compromised executive functioning [80]. Compounding ischemic intervals of 4-VO which correlate with more rapid or severe cognitive decline successfully recapitulate prominent outcomes of multi-infarct dementia, a leading contributor to VCI pathophysiology [65,81].

4-VO Model Considerations

Like the 2-VO transient global ischemia model, the 4-VO model employs temporary ischemia to evaluate the acute neural injury response. However, 4-VO intensifies cerebral hypoperfusion and subsequent damage with additional permanent vessel occlusion. Both models elucidate the brain's acute response to hypoperfusion yet fail to recapitulate the progression of insidious disease pathology present within the VCI disease spectrum. 4-VO studies primarily substantiate drastic CBF reductions, global neuroinflammation, metabolic disruption, and cognitive decline [16–19,21,64–68]. Interestingly, specific WM lesions are poorly characterized in 4-VO models, with literature primarily emphasizing neuronal population loss in memory-associated cerebral structures. These principal outcomes align with clinical VCI but more accurately recapitulate cerebral infarction and reperfusion injury marked by neuronal apoptosis, proliferative neuroinflammation, and free radical generation within the ischemic penumbra [82,83]. Rodent model WM changes are primarily evaluated via

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histopathology, whereas clinically, magnetic resonance imaging (MRI) identifies WM lesions and cerebral volume discrepancies [84]. Gregory et al. evaluated T2-weighted (T2W) MRI changes following 4-VO ischemic injury in the rat, but the authors note challenges with rodent MRI such as lower resolution, false negative findings, and difficulty isolating structural subfields which may limit model reproducibility [12]. In fact, neither MRI nor laser doppler or speckle imaging are well utilized in 4-VO VCI models, thus greatly reducing the translatability of a major vascular dementia diagnostic component. Lastly, the 4-VO model is further limited by its extreme neurologic and ataxic rates (77%), proportional to ischemic degree [18]. In one study, a 20-minute ischemic injury produces a 27.3% perioperative mortality rate with only 50% of the cohort surviving the 14-day study [16]. The close proximity of the vertebral arteries and the spinal cord may make it more difficult to determine if neurological deficits and higher mortality rates are secondary to the severity of the 4-VO procedure itself or incidental involvement of the spinal cord [85].

2.2. Chronic Global Ischemia

2.2.1. Bilateral Common Carotid Artery Occlusion (BCCAO)

While transient ischemic models such as 2-VO and 4-VO enable acute-phase evaluation of cerebral ischemia, chronic models have been developed to recapitulate progressive VCI pathology. Bilateral common carotid artery occlusion (BCCAO) is a well-characterized surgical VCI animal model, generating robust histopathological and cognitive outcomes following CCH induction.

Chronic global hypoperfusion in the BCCAO model is achieved using fine suture material to permanently ligate both common carotid arteries [86–90]. The rat is preferential for this model over the mouse due to its well-developed Circle of Willis cerebral vasculature which permits ischemia but inhibits severe cerebral infarction [91]. The mouse Circle of Willis is poorly adapted with a complete structure present in only 10% of mice and limited to specific strains [92,93]. BCCAO consistently instigates rapid and drastic reductions in global CBF and perfusion in rats. Schmidt-Kastner et al. showed that hippocampal CBF fell to 0.75±0.06 ml/g/min (75% of sham) and the temporal cortex CBF was reduced to 1.32±0.17 ml/g/min (57% of sham) 7 days after occlusion [94]. Choy et al. evaluated CBF alterations using continuous arterial spin labeling (ASL) MRI, notating a decrease in CBF in the cortex, hippocampus, and thalamus [86]. CBF in these regions, however, was restored to insignificant differences from sham 6 months later [86]. This vascular compensation is a natural limitation of rat VCI models due to their innate hemodynamically adaptive Circle of Willis which allows compensatory blood flow through basilar communicating arteries. While compensatory anastomoses is noted in clinical vascular dementia data, the incomplete human Circle of Willis challenges vascular compensation for frontal lobe ischemia, whereas the complete rodent Circle of Willis more readily restores global CBF in response to ischemic injury or persistent hypoxia [95]. As such, angiogenesis and collateral vascular remodeling may offer promising therapeutic targets.

GFAP is often used as an indicator of astrocyte immunoreactivity [89]. Prominent populations of GFAP+ astroglial cells in the cortex, corpus callosum, and internal capsule arise as early as 1 week and persists in the corpus callosum through 6 months post-operatively [89,96]. GFAP+ cell density is furthermore disproportionately increased in the CA1, CA3, and dentate gyrus of the hippocampus relative to other evaluated brain regions [97,98]. Astrocytic end-feet play a critical role in the neuron glucose-lactate shuttle and are crucial to neurometabolic integrity especially in the context of ischemia or cerebral hypoxia [99,100]. In a BCCAO-induced state of CCH, astrocyte remodeling contributes to downstream neuronal apoptosis, synaptic metabolic disarray, and secondary cognitive decline consistent with clinical disease [99,101,102]. A BCCAO study by Lee et al. noted an increased concentration of pro-inflammatory cytokines such as COX-2, IL-1, and IL-6 within the dorsal hippocampus specifically [103]. An acute increase in COX-2+ neurons of the hippocampus following ischemic induction throughout the CA3 and dentate gyrus indicates a reactive inflammatory response to the ischemic event itself rather than the chronic state of hypoperfusion [104]. COX-2-related prostaglandins may play a role in the inflammatory development of atherosclerosis, a risk

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factor associated with vascular dementia development [105,106]. Furthermore, the hippocampal endothelial cells are more susceptible to degradation than other brain regions, which is critically important given the increased global proliferation of pro-inflammatory cytokines following BCCAO [103,107,108]. Neuroinflammation in chronic hypoperfusion models like BCCAO can be studied longitudinally to evaluate how specific regions are affected and what down-stream effects chronic inflammation may have on histology, metabolism, and cognitive function in VCI.

As a central immune cell, microglia are largely responsible for the recruitment and release of pro-inflammatory cytokines in the brain [109]. Microglia are recruited and rapidly upregulated within 20 minutes of BCCAO-induced ischemic injury [34,88,104]. Marked gliosis, and the subsequent development of a glial scar, topographically align with MRI regions of interest, particularly the striatum [110]. Persistent microglial activation indicates ongoing, perhaps progressive, neuroinflammation in response to CCH. In one study, CD4+/CD8+ lymphocytes (a subset of T cells with enhanced cytokine production) were present within the optic tract, internal capsule, caudoputamen, anterior commissure, and corpus callosum from 1 hour to 90 days following complete vessel ligation [88]. These findings align with elevated cerebrospinal fluid levels of both CD4+ and CD8+ cells in both mild VCI and AD patients, with CD8+ T-cells most strongly correlated with clinical neuropsychological deficits [111]. Using the BCCAO model, Iba-1+ microglial activation was most densely present in WM, specifically the corpus callosum, internal capsule, and hippocampus [88,98]. Additionally, WM vacuolization on Kluever-Barrera staining was increasingly present in the corpus callosum and optic tract 14 days following vessel occlusion [112]. Numerous studies report optic tract degradation as a key BCCAO model limitation [96,113]. Farkas et al. reported 50% astrocytic disintegration in the optic tract with an accompanying 10-fold increase in microglial density as well as myelin sheath irregularities [96]. The optic tract susceptibility to ischemic damage is largely attributed to the rodent WM architecture with both the corpus callosum and optic tract containing much of the rodent's more limited WM density and the common carotids serving as the optic tract's main vascular supply [114]. Using the BBCAO model provides an opportunity to study the complex, synergistic interactions of neuroinflammation and WM damage that is persistent in VCI.

The high incidence of basal ganglia WM hyperintensities in clinical vascular dementia neuroimaging is recapitulated in the BCCAO model, making it a reliable model to target the therapeutic window of ganglia WM loss and its consequential altered striatal MRI and histological abnormalities [110,115,116]. WM lesions develop secondary to ischemic injury which may involve acute ischemic infarction, chronic small vessel disease, or mixed pathology. Within 24 hours of BCCAO-induced ischemia, T2W MRI reveals unilateral areas of focal and acute damage to the striatum with bilateral lesions by 10 days [110,116]. These findings are consistent with altered T2W distribution in human vascular dementia pathology [117,118]. Typical lesions in clinical VCI often occur within the subcortical frontal WM and basal ganglia, with strategic infarcts focused in watershed areas surrounding the anterior, middle, and posterior cerebral arteries [115,119,120]. Furthermore, fractional anisotropy (FA) values are lower in the frontal cortex, thalamus, optic tract, and hippocampus in BCCAO rats versus sham at 24 hours, indicating disorganized fluid movement from myelin fiber degradation or vessel lesioning [110,121]. Histologically significant cerebral tissue (glial scarring and profuse gliosis) correlated with foci of greater axial diffusivity (AD) and increased FA, particularly within the striatum by 12 weeks post-ischemic induction [110]. Additionally, diffusion weighted imaging (DWI) MRI revealed elevated apparent diffusion coefficient (ADC) signaling in BCCAO rats 3 days following occlusion, indicating free fluid movement from WM lesions and/or BBB [122]. Similarly, there was a positive association between intima-media thickness of the carotid arteries and the temporal ADC which is correlated with greater WM hyperintensity [123]. Consistent with findings from Sood et al. using the BCCAO model, poor patient performance in neuropsychological memory and abstract reasoning is also associated with higher ADC in clinical cases [122,123]. Use of the BCCAO model in organisms with complex, gyrencephalic WM architecture

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could be invaluable for studying disease progression and therapeutic intervention windows due to the similarities even noted within lissencephalic animals.

The hippocampus is a largely preferred region of interest when evaluating histological changes in BCCAO models due to its vulnerability to ischemia and its role in memory formation and retention [91,113,121,124]. Most specifically, the CA1, CA3, and dentate gyrus regions are sensitive to ischemic injury with apoptotic and necrotic pyramidal neurons observed from 2-12 weeks following vessel ligation [90,110,121]. Hippocampal atrophy is considered an early diagnostic hallmark in AD and is implicated in subcortical vascular dementia, though to a lesser degree [124,125]. It is, therefore, important to consider mixed-pathology dementia when evaluating hippocampal outcomes in VCI animal models [107,125]. In addition to region-specific neuronal apoptosis, hippocampal cellular metabolism of glucose and other energy substrates at the synaptic level was compromised in a chronically hypoperfused brain [113]. These findings expand upon the acute metabolic imbalances noted in both 2- and 4-VO models [14,19,53,54]. While glucose concentration was elevated at 24 hours in the 4-VO model, notably persistent glucose elevations at 3 weeks in the BCCAO model indicates neurometabolic malfunction secondary to CCH and ischemia [19,113]. Wang et al. noted an increase in the quantity of silent synapses (post-synaptic AMPA-silent) alongside reduced dendritic spine density in the hippocampal CA1 region following BCCAO [126]. The accumulation of extracellular glutamate may precede the spontaneous generation of AMPA-silent synapses, leading to progressive cognitive decline [126,127]. Additionally, Ni et al. reported significantly decreased circulating acetylcholine (by 14.9%) in the striatum 1 month following BCCAO [128]. By 4 months, acetylcholine concentrations decreased by 24.9% in the striatum, 21.2% in the cortex, and 14.5% in the hypothalamus as compared to sham [128]. Furthermore, circulating choline, an acetylcholine precursor, decreased within the striatum, cortex, hypothalamus, and hippocampus, indicating a high likelihood of broad cholinergic dysfunction rather than acute neurotransmitter depletion [128,129].

BCCAO model functional testing, particularly at chronic timepoints, correlates histopathological changes with progressive cognitive decline [130]. At 60-90 days post-operatively, non-spatial working memory impairment was indicated by poor performance in novel object recognition testing [91,97,113]. Choi et al. demonstrated a 52.6% preference for the novel object, indicating random object choice rather than memory recollection [97]. While impaired memory is a symptom of broad VCI presentation, it is no longer considered a principal implication of cognitive symptomatology [131]. Moreover, latency in the Morris water maze test and increased error occurrence in the 8-arm radial maze indicated impairment of both spatial working and reference memory [90,91,130,132]. Increased errors in 8-arm radial maze were apparent by 24 hours after occlusion and subjects remained impaired through 21 days [133]. Poor performance in the Y-maze was also observed at 60- and 90-days following BCCAO procedure. Performance discrepancies were also perceived at 30 days, but without statistical significance, thus suggesting a delayed onset of spatial working memory impairment following chronic blood flow reductions [113]. Bennett et al. specifically correlated TUNEL-positive CA1 pyramidal neurons (i.e., apoptotic and late-stage necrosis) with Morris water maze and 8-arm radial maze errors at 27 weeks ($r=0.66$ and $r=0.86$, respectively) [90]. Spatial memory impairment worsens with increased study duration, supporting the hypothesis that chronic CCH causes more severe cognitive deficits than acute [91]. Poor performance in the elevated T-maze 30 days following vessel occlusion implicates dysfunction of inhibitory avoidance memory in the BCCAO rat [105]. Interestingly, a study by Atucha et al. evaluated inhibitory avoidance discrimination using a foot shock prior to and following the administration of a noradrenergic stimulant finding enhanced memory following treatment [134]. Given both the proliferation of glutamate following 2-VO occlusion and the glutamate-mediated amplification of noradrenergic signaling, the continued exploration of neurotransmitter-associated cognitive outcomes in animal VCI models may reveal novel treatment targets [134,135]. Evaluation of reference and working memory 16 months following BCCAO yielded a significant deficit in both memory types [130]. By 16 months, sham rats begin to display memory decline attributed to normal aging. The significantly poorer performance of BCCAO rats indicates a synergistic effect of hypoperfusion with aging to

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accelerate cognitive decline. Importantly, the basal ganglia is also involved in task-relevant memory utilization and emotional regulation, the exploration of which may be important in future studies to connect cognitive decline with basal ganglia-specific WM ischemic injury [136]. Additionally, impaired performance in fear and anxiety-dependent tasks correlate with neuropsychological changes in clinical vascular dementia symptomatology [91,137]. The elevated T-maze in rodent models examines inhibitory avoidance behavior relative to innate anxiety habits [138]. Abnormalities in elevated T-maze performance were also noted in stroke-prone hypertensive rats in a study by Ueno et al., suggesting a possible connection between vascular degeneration and behavioral changes [139]. Clinical findings note higher Neurobehavioral Rating Scale scores in vascular dementia patients as compared to AD patients, with higher incidence of anxiety/depression and behavioral abnormalities [137]. Late-term onset of memory impairment in animal models highlights the need for a CCH model which can recapitulate the progressive decline seen in clinical VCI to more thoroughly investigate disease progression and mechanistic pathology.

BCCAO Model Considerations

A complete evaluation of vascular dementia pathophysiology as it relates to outcomes noted in VCI animal models considers both acute injury response to ischemia as well as the chronic development of cellular and behavioral alterations. However, restitution of global CBF at chronic timepoints denotes a natural blood flow compensatory mechanism in rodents that poorly replicates human disease pathophysiology. Given the biologically advanced rodent Circle of Willis, CBF compensation likely occurs through dilation of basilar arteries and posterior communicating arteries [86]. Significant differences in both length and tortuosity of the vertebrobasilar vascular system is present on magnetic resonance arteriography by 1 week and consistent through 12 weeks in BCCAO rats [110]. Alterations in existent vasculature is furthermore accompanied by basilar angiogenesis [110]. This vascular remodeling allows rodents to overcome some CCH symptomatology; however, it may indicate an interesting therapeutic target with further research surrounding compensatory angiogenesis.

A significant proportion of WM lesions occur in the optic tract to a greater degree than other brain regions of interest [88,96,110,113]. A loss of myelination fibers, vacuolization of WM tracts, and reductions in retinal neuron populations were evident in BCCAO rats after 12 weeks of occlusion [110]. Due to the degradation severity in the optic tract, outcomes of functional testing, most of which require visual perception interpretation of cues, objects, and landmarks, must be considered in the context of compromised visual acuity. The 2-VO model, for example, has been applied to visual ischemic research context, such as diabetic retinopathy, but the continuation of the BCCAO model in VCI research requires some alteration to either preserve visual integrity or evaluate cognition without a dependence on visual cues [91]. Interestingly, however, visual impairment has been identified in AD pathophysiology with amyloid-β plaque deposition in the lens, nerve fiber degradation, axonal loss in the optic nerve, visual cortex pyramidal cell loss, and the presence of neurofibrillary tangles and tau pathology in the visual cortex [140,141]. Reduced visual function most certainty correlates with impaired cognitive and behavioral outcomes and quality of life in vascular dementia and AD patients [142].

2.2.2. Bilateral Common Carotid Artery Stenosis (BCAS)

While the BCCAO model of carotid ischemia is well tolerated in rats, the procedure is rather severe in mice and the survival rate is significantly reduced [143]. Capitalizing on the poorly developed mouse Circle of Willis allows greater translatability to human disease, necessitating the adaptation of the BCCAO procedure to induce stenosis rather than total occlusion. Bilateral common carotid artery stenosis (BCAS) follows the same principal procedure as BCCAO in approaching the common carotid arteries via ventral incision, after which the vessels are separated from their sheaths and surrounding tissue. Rather than suture ligation, specialized micro-coils are twined around the exposed carotid arteries, just proximally to the carotid bifurcation, narrowing vessel luminal diameter to generate sustained stenosis and secondary cerebral blood flow reductions.

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The micro-coils are made of specialized piano-wire material available in varying internal diameters, including 0.16, 0.18, 0.20, and 0.22mm. The 0.18mm internal diameter micro-coils are preferred as they allow blood flow reduction with lower mortality rates than 0.16mm coils or occlusion [22,23]. Reductions in CBF are not adequately achieved in the BCAS model when using a 0.22mm internal diameter micro-coil [22,144]. At 2 hours post-operatively, the 0.16mm internal diameter coil group, however, more severely restricted CBF to 51.4±11.5% of baseline when evaluated with laser doppler flowmetry [144]. The acute and severe CBF restriction using the 0.16mm coil in mice resulted in extreme mortality rates equivalent to those of the BCCAO model when applied to mice [16,143,144]. Furthermore, disproportionately high mortality rates (up to 75%) have been noted in 0.16mm groups primarily resultant from large and severe cerebral infarcts [22,145]. The surviving animals with 0.16mm coils displayed neurologic deficits and akinesia upon regaining consciousness [144]. In addition to drastic CBF reductions, the 0.16mm internal diameter coils generated ischemic and apoptotic neurons in the cerebral cortex, hippocampus, and basal ganglia with parietal cortex cerebral infarcts in 60% of the surviving 0.16mm group mice [144]. The most effective coil size in the BCAS model, 0.18mm, sufficiently reduced CBF and generated secondary pro-inflammatory pathways and downstream neuronal degeneration while normalizing mortality rates to 15% [143]. At 2 hours post-procedure, CBF was reduced in 0.18mm coil group mice to ~60±10% of pre-operative baseline across studies [3,132,144,146,147]. CBF recovery trended back toward baseline by 1 day (72.4±17.3%), but remained depressed relative to baseline and failed to recover as rapidly as transient occlusion and BCCAO models [148]. CBF was gradually restored to ~80% of baseline by 30 days [146,148] and to 85±8.7% by 60 days [147]. Given the poorly developed mouse Circle of Willis, CBF restoration is hypothesized to recover via collateral angiogenesis or cerebral anastomosis [22]. CBF measurements obtained via ASL MRI rather than laser doppler flowmetry enable perfusion estimates of subcortical areas in addition to the cortical parenchyma. ASL revealed a more drastic and chronic CBF reduction to 50% of baseline at 14 days following BCAS with persistent reductions in thalamic and corpus callosum CBF at 50-60% of baseline at 3 months post-operatively [146,149]. Radial diffusivity (RD) was significantly increased in the hippocampus, corpus callosum, internal capsule, and striatum after 6 weeks of stenosis, indicating progressive myelin loss [150]. Similarly, FA was altered in the frontal, temporal, and parietal lobes and in periventricular WM [151]. Thus, the persistent and moderate reduction in subcortical CBF in BCAS models reliably recapitulates CCH as a hallmark of VCI pathophysiology.

Despite more conservative CBF reductions by BCAS as compared to BCCAO models, reductions in viable neuron populations and evidence of pyknosis and apoptotic neuronal signaling pathways are still apparent. In identical cortical slices, shams retained 85-90% viable neurons while identical regions of BCAS mice showed significantly diminished populations with 40% viable cells [23]. When evaluated 8 months later, BCAS produced pyknotic neurons throughout both the cerebral cortex and hippocampus with preferential hippocampal atrophy [147,152]. Cholinergic fiber disorganization and reduction was also present, suggesting compromise in neurotransmitter system integrity and reduced overall synaptic function [147]. A study by Ni et al. demonstrated significantly reduced acetylcholine levels in the striatum at 1 month following vessel ligation and in the striatum, cortex, and hippocampus at 4 months [128]. A later study by Tanaka et al. correlated choline acetyltransferase (ChAT) and acetylcholine receptor deficiencies with poor discrimination learning task performance after 6 weeks of CCH [153]. Post-mortem evaluation of patients with AD, multi-infarct dementia, or a mixed pathology dementia also revealed significantly reduced ChAT activity in the temporal, frontal, and hippocampal regions [154]. Acetylcholine is synthesized by both neurons themselves and non-neuronal cerebral cells, specifically astrocytes, which are also significantly dysregulated in BCAS and BCCAO VCI models [143,146,155,156]. Furthermore, muscarinic acetylcholine receptors are present both pre- and post-synaptically and are involved in heterogenous brain functions [157]. Interestingly, muscarinic acetylcholine receptors can reduce glutamate release from cortical and striatal synapses [157]. As such, the BCAS model may serve as a reliable and

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reproducible model through which cholinesterase inhibitors or cholinergic agents may be tested for therapeutic efficacy [158,159].

In addition to neuronal density reduction, myelin staining intensity was reduced in 0.18mm coil groups by 30 days following BCAS , most notably within the corpus callosum, caudoputamen, internal capsule, and optic tract, with myelin fibers appearing disordered and accompanied by frequent WM vacuolization throughout stained histological slices [144,148]. WM lesions were not histologically apparent until 14 days, at which point rarefaction was minor, but noted in the corpus callosum, striatum, and internal capsule [132]. Severe lesions were present by 30 days and indicate a progressive loss of WM integrity following CCH induction [144]. Additionally, WM lesions were specifically noted in the hippocampus and corpus callosum of BCAS mice at 28 days with frequent and severe vacuolization, axonal loss, and reductions in CA1 hippocampal volume [23].While no gray matter infarctions or hemorrhages were noted in 0.18, 0.20, or 0.22mm groups, partial cortical lesions were present in 0.16mm groups at 30 days [144,148]. Additionally, foci of glial accumulation with neuronal apoptosis and CA1 neuronal density loss accompanied vascular lesions in 0.16mm groups [144]. Microglial populations increased from 7-30 days across all coil sizes, particularly those labeled for MHC class II antigen, which is implicated in chronic neurodegeneration [144,160]. GFAP+ astrocytes were slower to activate, becoming significantly increased from 14-30 days in the 0.18mm groups with correlation to regions of high density WM loss [144]. While glial cell activation was acutely elevated, but regressed to mild intensity 3 days following reperfusion in 2-VO models, the CCH induced in BCAS models allows for gliosis to remain increased, thus more accurately recapitulating the chronic gliosis of VCI and vascular dementia pathology [34,45].

As endothelial adhesion molecules involved in immune regulation, ICAM-1 and VCAM-1 play a crucial role in signaling positive feedback loops for microglial and astroglial recruitment to areas of vascular ischemic injury or hypoperfusion [161]. Increased gene expression of both ICAM-1 and VCAM-1 was persistent through 28 days following BCAS procedure, correlating with increases in both GFAP+ cell density and Iba-1+ intensity at corresponding timepoints [23]. Increased adhesion protein expression contributes to BBB degradation and cyclical neuroinflammation [33,49,50]. MBP was drastically reduced in the hippocampus and corpus callosum 28 days after BCAS, consistent with WM lesion foci and abnormal myelin staining [23,48,144]. Concomitant GFAP+ cells and astrocyte proliferation were consistent with human vascular dementia pathology in which MMP-2 and GFAP+ cells accumulated around vascular infarcts and diffusely throughout WM [162,163]. Serum MMP-9 was also found to be elevated in patients with cognitive impairment in contrast to 2-VO models in which greater concentrations of MMP-2 compared to MMP-9 were found at acute timepoints [33,51,164]. Importantly, the consistent proliferation of oxidative stress markers in the BCAS model highlights the role of oxidative stress and neuroinflammation in human VCI and vascular dementia disease pathology. While acute elevations in cytokines and gliosis indicate neural reactivity to ischemic injury, the persistence of such factors correlate with chronic and progressive oxidative stress in patients of vascular dementia and AD, in which oxidative stress marker concentration is proportionally related to disease progression [165]. Nitric oxide (NO), for example, is a bimodal intercellular messenger that, when in excess, is neurotoxic and triggers mitochondrial damage and cellular apoptosis [166]. 3 weeks following BCAS procedure, both AMP and ATP were persistently elevated 8-fold from baseline, indicating impaired mitochondrial function and neurometabolic dysregulation [133]. As a neurotransmitter under CCH, post-synaptic NO triggers glutamate release and modulates synaptic plasticity and long-term potentiation [167]. Similarly, persistently prolific ROS and associated enzymes contribute to an apoptotic neuronal signaling cascade and endothelial tight junction claudin-5 and occludin degradation [168,169]. In a study by Holland et al., claudin-5 levels were directly assessed via enzyme-linked immunosorbent assay at 1 and 6 months following BCAS [170]. Claudin-5 levels did not significantly differ from sham at 1 month, but were significantly decreased by 6 months [170]. Cytokines such as TNF-α bind directly to neurons, triggering apoptotic neuronal pathways. TNF-α is elevated in both clinical AD and vascular dementia pathology [171]. In BCAS models, TNF-α was increased from 1 day to 4 weeks post-operatively, the direct stimulation

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of which correlates to a reduction in claudin-5 and occludin in cerebral endothelial cell populations [145]. These tight junction proteins are degraded by deleterious, upregulated MMPs, which, in turn, triggers neurovascular uncoupling and BBB disruption [172–174]. The intraperitoneal injection of Evans blue dye at 1, 3, 7, and 42 days following BCAS procedure by Yang et al. demonstrated tight junction disruption which allowed infiltration into the brain parenchyma, with Evans blue extravasation at all evaluated timepoints [175,176]. Modeling the oxidative and inflammatory cascade following CCH is vital in identifying the key factoring perpetuation the regenerative cycle that leads to downstream tissue death and subsequent cognitive abnormalities.

The perpetuation of neuroinflammatory cytokines, astrocytosis, microgliosis, and progressive WM loss synergistically contribute to cognitive decline. Deficits in reference and spatial working memory have been reproduced through BCAS models [22,177]. Several studies have also demonstrated working memory impairments in the 8-arm radial and Y-maze with marked increases in committed errors at 30 days [145,147,148,156]. Some mice were even unable to complete the 8-arm radial maze within the allotted time [177]. Yang et al. reported BCAS mice committed to 20% more initial entry errors in the 8-arm radial maze versus sham [176]. Relative to short-term memory, Khan et al. later showed impairments in BCAS non-spatial working memory in novel object recognition testing which correlated with prefrontal cortex histological abnormalities at a comparative timepoint [23]. Changes in neural activation in clinical VCI testing often depends on working memory demands, thus correlating cognitive findings of BCAS models with patient outcomes [178,179]. While the deep cortical WM most prominently impacted by CCH primarily correlates with executive function and working memory, gait abnormalities and imbalance present in clinical vascular dementia pathology indicate injury to the motor fibers responsible for normal ambulation [180]. A common neuropsychological clinical finding is the inability to walk-and-talk, or perform a dual motor and linguistic task [181]. At 30 days following coil placement, Shibata et al. did not obtain significant differences between BCAS and sham groups in sensorimotor reflex tests, gaiting, nociception, or wire hang and rotarod tests for motor coordination [148]. Importantly, the cognitive decline noted among mice is not accompanied by sensorimotor or coordination deficits at acute timepoints, but instead develops by 3 months following vessel stenosis with significant discrepancies present in beam testing and stance percent of the gait cycle [147,148]. The addition of motor and discriminatory dual tasks to the BCAS model may strengthen the relationship of CCH-induced pathology and functional outcomes [182]. Gait abnormalities and sensorimotor deficits are considerable symptoms of vascular dementia and AD, however, and the inability of BCAS models to produce motor deficits currently limits translatability [181].

BCAS Model Considerations

The BCAS mouse model adequately reduces CBF, generating a CCH state without the severe optic tract WM rarefaction and myelin degradation as seen following BCCAO [110,144]. With optic tract integrity largely maintained, the robust discrepancies in cognitive testing outcomes can be interpreted with greater confidence than 2-VO, 4-VO, or BCCAO models which compromise the visual pathway with greater severity. Additionally, the milder reduction in CBF following BCAS as compared to BCCAO models and slower onset of secondary neuroinflammatory and immune cascades more accurately recapitulates patient VCI disease progression or vascular dementia pathophysiology. However, it remains more severe when considered against the true chronicity of the disease. Furthermore, endogenous vascular repair mechanisms may contribute to eventual CBF restoration in BCAS models due to the young age (10-12 weeks old) of rodents typically enrolled [22,152]. Given the prevalence of age as a VCI risk factor, young animal models introduce confounding factors that may reduce BCAS model applicability and translatability.

2.2.3. Bilateral Common Carotid Artery Gradual Occlusion (BCCAGO)

Bilateral common carotid artery gradual occlusion (BCCAGO) involves the application of a specialized ameroid constrictor (internal diameter 0.5-0.75mm) to one or both common carotid arteries [132,183]. The ameroid constrictor consists of a stainless-steel ring filled with a hygroscopic

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casein material designed to absorb the fluid of the vessel it contains and swell until the vessel reaches near or total occlusion up to 28 days following constrictor placement [183,184]. Some studies employ an asymmetrical approach, placing an ameroid constrictor around one common carotid artery and a micro-coil (0.18mm) around the other [183,185]. Common carotid artery stenosis can also be achieved using larger-diameter ameroid constrictors (0.75mm internal diameter) to reduce luminal diameter rather than completely occlude the common carotid artery [186].

The BCCAGO model eliminates the drastic post-operative acute phase of CBF reduction with CBF remaining at baseline immediately following the procedure and not declining until 1-3 days later [132,185,187]. Unlike BCCAO and BCAS models, which exhibit both drastic acute CBF reductions and eventual restoration of CBF, BCCAGO models demonstrate a continuous reduction in CBF [183–185,187]. BCAS, for example, demonstrated an acute CBF reduction to 62.9±18.5% of baseline at 2 hours with recovery to 81.7%±4.0% at 1 month, while BCCAGO CBF declined from 83±5% at 1 day to 49±3% of baseline at 33 days [147,186]. In an asymmetrical BCCAGO study by Hattori et al., CBF declined to 87.2% of baseline on the ipsilateral constrictor side at 1 day and continued to decrease to 73.4% of baseline by 28 days [184]. A BCCAGO model using bilateral ameroid constrictor placement also noted CBF preservation compared to baseline at 2 hours, 1 day, and 3 days at 98.2±0.1%, 87.5±2.2%, and 85.1±3.9%, respectively. Similar findings between bilateral and asymmetrical ameroid constrictor placement may suggest hemispheric symmetry is not crucial to the development of global ischemic injury.

CBF reductions in BCCAGO models are proportional to both the internal diameter of the constrictor and the age of the animal. Notably, the placement of 0.5mm ameroid constrictors around both common carotid arteries resulted in elevated mortality rates in mouse models (58.8% by 28 days) [187]. In 1-year old mice undergoing bilateral 0.5mm constrictor placement, only 20% of mice survive beyond 15 days [188]. Additionally, CBF declined far more drastically in 1-year old cohorts versus 10-12-week-old animals [188]. Because VCI risk increases proportionally with age, exaggerated CBF responses to carotid stenosis in older rodent models further support age as a key contributor to its pathophysiology [189].

CBF is progressively reduced at both a cortical and subcortical level at 14-28 days when evaluated via ASL MRI in BCCAGO models [184]. Similarly, clinical evaluation of CBF using ASL demonstrated a reduction in thalamic, temporal lobar, and hippocampal CBF with correlations to WM hyperintensities and neuropsychological outcomes in patients of small vessel ischemic disease and mild cognitive impairment [190]. At 28 days post-surgery, bilateral ameroid constrictor groups demonstrated global CBF rates of 70±5% [183,187]. But, subcortical WM appeared more sensitive to chronic ischemic injury with subcortical and cortical CBF at the bregma level reduced to 17% and 24% of baseline at 28 days, respectively [184]. Subcortical WM behaves similarly in acute post-stroke pathology, in which WM lesions predominantly occurred in deeper subcortical WM tracts [184,191]. After 8 days of gradual occlusion, WM hyperintensities were apparent within the corpus callosum, caudate putamen, internal capsule, and hippocampal fimbria on DWI and T2W sequences [184]. WM hyperintensities were correlated with topographically equivalent subcortical infarcts, with most infarcts occurring within the caudoputamen and corpus callosum [187]. Given the absence of MRI evaluation in the majority of VCI animal models, the significance of these subcortical lesions is difficult to attribute to the BCCAGO surgical model itself as they may be present in other models in which CBF evaluation is limited to cortical tissue.

BCCAGO models produce a comparatively lower level of gray matter damage, and subsequent metabolic changes, than other models such as BCCAO and BCAS [132]. Cerebral infarcts were identified via T2W MRI in numerous studies, particularly within the corpus callosum, caudate putamen, internal capsule, and hippocampus from 8-32 days post-surgery [184,192]. Hippocampal neurons appeared pyknotic and necrotic at 32 days ipsilateral to the ameroid constrictor, particularly within the CA1 and CA2 regions [192]. Distinct from the CA1 and CA3 regions, which are selectively injured in BCCAO and BCAS chronic models, the CA2 region of the hippocampus is involved in social recognition memory and may be significant in the context of BCCAGO model behavioral and

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cognitive changes [23,90,110,193]. Furthermore, the integrity of the optic tract is largely preserved in BCCAGO models with far fewer WM lesions noted 28-32 days following constrictor placement when compared to BCCAO models, strengthening the argument that cognitive changes in this model stem from CCH rather than visual compromise [183,194]. At 28 days, degenerative neurons displayed greater fluorescence intensity in the cerebral cortex, dorsal striatum, and CA1 hippocampus post-BCCAGO versus sham [194]. Reductions in healthy neuron populations within these brain regions may suggest reduced synaptic function necessary to perform executive function tasks, maintain healthy processing speed, and sustain attention. With rising diagnoses of vascular-related neurodegenerative diseases beneath the VCI umbrella, such as cerebral small vessel disease, vascular dementia, Parkinson's disease, and multiple sclerosis, the milder, progressive cerebral changes of the BCCAO model may provide a useful experimental framework [127,195,196].

Neuroenergetic disruption in vascular dementia-specific VCI is the result of an unsteady energetic flow to the brain, resulting in neural activity and functional connectivity deficiencies. As previously stated, BCCAGO models exhibit distinct neuronal loss, but ChAT+ neurons, in particular, were significantly reduced in both the dorsal striatum and medial septum of BCCAGO groups compared to sham, suggesting chronic cholinergic neuron deficiency [186,194]. Persistent cholinergic deficiency is generally accepted as a pathophysiological contributor to vascular dementia with both Goffries and Perry et al. reporting reduced ChAT+ neurons in brain tissue of vascular dementia patients [154,197,198]. Zhai et al. found reduced striatal nicotinic acetylcholine receptor density at 8 months post-BCCAGO; however, muscarinic Ach receptor density showed no significant differences between sham and constrictor groups [199]. It is known that muscarinic Ach receptor populations are largely preserved in AD while nicotinic Ach receptors are significantly and consistently reduced in cortical tissue of AD patients [200]. The extent of nicotinic cholinergic disruption in vascular dementia, however, remains ambiguous, as some studies demonstrate subcortical nicotinic receptor depletion while others note discrepancies only in "mixed" and "pure" AD pathology [201,202]. In conjunction with BCCAO-induced AMPA-silent synapse development, however, impairment of nicotinic Ach receptors in BCCAGO may indicate a pertinent role of synapse failure and neurovascular uncoupling as a driving force behind cognitive decline and should be explored within this model [203,204]. Sparse BCCAGO literature underscores the need to clarify neurotransmitter and neurometabolic roles in this model. Broader application of BCCAGO to assess CCH-driven neuroenergetic shifts may illuminate mechanisms of cognitive decline beyond neuronal apoptosis and acute ischemic WM injury.

The BCCAGO model is uniquely able to recapitulate WM lesions and associated-glial cell abnormalities due to the use of gradual occlusion techniques. At 32 days post-operatively, demyelination was observed throughout the corpus callosum, concomitant with GFAP+ cell proliferation, Iba-1+ gliosis, and glutathione S-transferase (GST-π+ oligodendrocyte loss [183,192,199]. Zhai et al. specifically noted decreased myelin stain intensity at 2 (0.82±0.04 vs. 1.00±0.06, respectively) and 6 months (0.74±0.10 vs. 0.91±0.07, respectively) when compared to shams [199]. Hippocampal NeuN+ cells decreased in only 25% of BCCAGO mice receiving a 0.75mm internal diameter constrictor with a 0.18mm micro-coil, suggesting only a moderate incidence of hippocampal degeneration [183]. Additional studies demonstrate prominent WM vacuolization and hippocampal neuron loss within the CA1, CA3, and dentate gyrus of the hippocampus in 0.5mm constrictor groups [185]. Discrepancies in histological results may be due to the internal diameter of the ameroid constrictor applied. Additionally, axonal injury and prominent corpus callosum atrophy are notable in 0.5mm ameroid constrictor models [185]. Axonal injury in VCI pathology is generally attributed to Wallerian degeneration of cortical pyramidal neurons to the corpus callosum [205,206]. Tomimoto et al. noted prominent corpus callosum atrophy without histological lesions in AD patients, but emphasized only mild corpus callosum atrophy with deep WM lesions in patients with small and large vessel ischemic disease [205]. Severe body atrophy and deep WM lesions in BCCAGO models adequately recapitulate those seen in clinical patients, supporting their efficacy as a model of mixed-pathology dementia.

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BCCAGO models aim to correlate CBF reductions and histological damage with overt and progressive cognitive impairment, particularly proportional with the severity of disease. Spatial working memory deficits were apparent at 28 days following ameroid constrictor placement, evidenced by discrepancies in exploratory alternation between Y-maze arms [132,183,184,188]. Consistent with low incidence of hippocampal neuron loss, equivalent performance in the Morris water maze between sham and BCCAGO groups indicated retention of hippocampal-dependent reference memory at the same timepoint [183]. Meanwhile, Fagerli et al. reported no significant Y-maze discrepancies or neuronal population changes between sham and BCCAGO mice at 33 days post-procedure using 0.75mm internal diameter constrictors [186]. In future studies, greater diameter constrictors may require longer survivability timepoints to achieve clinically comparable histological and cognitive outcomes. Despite the lack of statistical significance, some obvious differences in Morris water maze performance between sham and 28-day post-BCCAGO groups, such as longer escape latency and reduced swimming speed, indicated a reduction in typical motivation behavior [188]. Interestingly, Hattori et al. reported reduced swimming speed in ameroid constrictor groups versus sham, which is not a common finding in other VCI models despite robust discrepancies in performance, path length, and time in target area [170,187,207]. BCCAGO mice exhibited reduced freezing in delayed tone fear conditioning, reflecting impaired anxiety-related behavior and aligning with the heightened impulsivity observed in vascular dementia patients [139,194,208]. Furthermore, poor performance in novel object recognition indicated that CCH impaired both recognition and declarative memory as well as innate exploratory behavior [194]. Novel object recognition testing may also be used to challenge and evaluate short- and long-term memory, as both forms of memory tasks rely on the medial temporal lobe [209,210]. Discrepancies in the novel object test not only in BCCAGO groups, but also across other surgical VCI models, indicated strong positive correlations between temporal lobe (e.g., frontal cortex and hippocampus) injury and both acute and progressive cognitive decline [23,91,97,113,186].

Interestingly, motor coordination, balance, and muscle strength were all implicated in BCCAGO mice at 28 days as indicated by both shortened latency to fall in rotarod and wire hang tests [183,188,199]. In a clinical cohort study by Duchowny et al., reduced grip strength was associated with poor memory test performance, volume of WM hyperintensity, and a vascular dementia diagnosis [211]. Hattori et al. recapitulated the neuromuscular weakness associated with VCI pathology by reporting significantly shortened latency to fall in the wire hang test at 28 days [187]. Furthermore, Mehla et al. demonstrated longer crossing times on the balance beam with greater incidence of foot slips at the same timepoint, thus suggesting decreased motor coordination and balance secondary to constrictor-induced CCH [194]. Motor coordination is associated with human vascular dementia pathophysiology in which lacunae and deep WM tract lesions in the frontal, parietal, and temporal cortices propagate reductions in executive function integrity, motor coordination, balance, and gait abnormalities [212,213]. Furthermore, a compromised basal ganglia may perpetuate both motor discrepancies and motivation or emotional regulation capacity [212]. Although injury-driven cerebral compensation and reorganization complicate linking cognition and motor function, BCCAGO models may help clarify the anatomical cand pathological correlations of VCI spectrum diseases.

BCCAGO Model Considerations

BCCAGO-induced gradual CBF reduction, with no spontaneous restitution, more reliably recapitulates human small vessel disease while generating abundant secondary histological and immunohistochemical injury data. The milder histological findings in BCCAGO groups suggest a greater impact of chronic oligemia on neuroinflammation resultant from subcortical CBF reductions rather than acute cortical ischemia [184,214]. In mouse studies, the model is constrained by high mortality, since survival beyond full constrictor occlusion is limited by the poorly developed Circle of Willis, yielding mortality rates similar to those that preclude BCCAO models [143,183,184,192]. However, models employing ameroid constrictors effectively reduce the incidence of confounding visual factors while demonstrating etiological mechanisms and pathophysiological changes with

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translatable symptomatology to human VCI. Specific WM tracts are implicated in studies applying the BCCAGO model which correlate most robustly with gradual CBF reductions and consequential deficits in learning, memory, and cognition. Furthermore, ameroid constrictor models note the development of gait abnormalities and muscular weakness, which is not apparent in most BCCAO and BCAS models. These findings may facilitate earlier diagnosis as gait abnormalities are predictive of clinical vascular dementia [215]. Gradual CBF reductions without compensatory restitution more reliably recapitulate CCH in human vascular dementia than BCCAO or BCAS models, which instead demonstrate acute drastic ischemic injury. While CCH model refinement has elucidated the heterogenous underlying mechanisms of progressive VCI disease relative to WM injury and neuroinflammatory cascades, most models still struggle to recapitulate gradual disease onset. The BCCAGO model adequately produces gradual and permanent CCH and demonstrates immunohistochemical consequences. While sufficient literature regarding BCCAGO models is presently limited, the BCCAGO model is promising as it offers reliable reductions in CBF, histological changes, and cognitive deficits. Future studies would benefit from the continued optimization of the BCCAGO model for predictability and translatability.

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Surgical Model	Species	CBF Reduction	WM Lesions	Histology	Neuroenergetic Disruption	Functional Deficits	Sources
2-VO	Rat, Mouse	Severe and acute (10-20% of baseline during occlusion → 40-50% of baseline following clip removal) with reperfusion → 80-90% after 5 minutes of reperfusion	WM-specific oligodendrocyte loss	Early striatal and cortical neuron loss with later CA1 hippocampal pyramidal neuron reduction, robust microgliosis acutely, prolific astrocytosis	Glutamate, GABA, and dopamine extracellular imbalance both intra- and post-operatively; decreased expression of hippocampal NMDA receptors	Acute discrepancies in spatial working and reference memory worsened by 13 months, impaired spatial learning	Abraham et al. 2000, Hartman et al. 2005, Heim et al. 2000, Petito et al. 1998, Sugawara et al. 1999, Wahul et al. 2018, Walker et al. 2010, Wei et al. 2008, Onken et al. 2012
4-VO	Rat	Severe and acute (6-14% of baseline during occlusion) with recirculatory overflow when allowed to reperfuse	Striatal lesions by 24 hours, hippocampal lesions by 72 hours with ischemic interval as short as 10 minutes	Significant neuron loss in CA1, CA3 hippocampal regions acutely following repeated ischemic intervals; increased MMP-2 and MMP-9 activity	Decreased glucose metabolism, cortical and hippocampal acetylcholine abnormalities, extracellular glutamate imbalance	Spatial working memory impairment, inconsistent motor dysfunction, seizures, high mortality with degree of injury and impairment proportional to duration of ischemic injury	Chung et al. 2002, Goto et al. 1990, Gregory et al. 2001, Irie et al. 2002, Iwasaki et al. 1996, Kim et al. 2023, Martins-Pereira et al. 2012, Neto et al. 2005, Pulsinelli et al. 1979, Schmidt-Kastner et al. 1989, Song et al. 2019, Sun et al. 2021, Yamaguchi et al. 2005
BCCAO	Rat	Drastic (35-45% of baseline acutely) with gradual recovery (60% of baseline at 2 weeks) and chronic normalization (= to sham at 6 months)	Diffuse WM vacuolization, de- and dysmyelination on MRI, subcortical infarcts, striatal T2W lesions as early as 24 hours	Hippocampal neuronal loss noted at 2 weeks and accelerated by 27 weeks, oligodendrocyte loss, robust astrocytosis, proliferative inflammatory cytokines, gliosis	Altered adenosine activity, impaired cortical glucose energy metabolism, cholinergic system dysfunction	Robust spatial and non-spatial working memory impairment, reference memory deficits, abnormal fear and anxiety-based behavior	Bennett et al. 1998, Cao et al. 2016, Cho et al. 2006, Choi et al. 2011, Choy et al. 2006, Farkas et al. 2004a, Farkas et al. 2004b, Farkas et al. 2007, Kimura et al. 2025, Leon-Moreno et al. 2020, Ni et al. 1995, Plaschke et al. 2006, Sarti et al. 2002, Schmidt-Kastner et al. 2005, Schmidt-Kastner et al. 2001, Sood et al. 2009, Serita et al. 2013, Tommoto et al. 2003, Tukacs et al. 2020, Wakita et al. 1994, Wang et al. 2020, Wang et al. 2016, Zhao et al. 2015
BCAS (0.18mm coil)	Mouse	Moderate (60% of baseline acutely) with gradual recovery (→ 80-1% of baseline by 30 days)	Severe optic chiasm and corpus callosum WM rarefaction, demyelination by 30 days, inconsistent hippocampal and cerebral cortex WM lesions, hippocampal atrophy	Significant cortex and hippocampal neuron loss, acute and chronic gliosis, astrocytosis, elevated oxidative stress markers	Impaired hippocampal glucose uptake by 6 months, persistent acetylcholine imbalance with cholinergic fiber disorganization, impaired ATP metabolism	Robust spatial and non-spatial working and recognition memory impairment, gait and sensorimotor discrepancies absent acutely but develop by 3 months	Bink et al. 2013, Hattori et al. 2016a, Holland et al. 2015, Ishikawa et al. 2023, Li et al. 2015, Maki et al. 2011, Nishio et al. 2010, Patel et al. 2017, Shibata et al. 2004, Shibata et al. 2007, Toyama et al. 2014, Wang et al. 2020, Weng et al. 2023
BCCAGO	Mouse	Gradual and progressive (insignificant at 1 day → 60% of baseline by 30 days)	Robust corpus callosum, caudoputamen, and hippocampal WM infarcts and vacuolization by 8 days, few lesions of the optic tract	Pyknotic and necrotic hippocampal, striatal, and cortical neurons by 32 days, oligodendrocyte loss, gliosis	Persistent cholinergic neurotransmitter deficiency and fiber disruption	Spatial and non-spatial memory impairment at later timepoints, impaired motor coordination, balance, and strength., abnormal fear and anxiety-related behavior	Elhassanien et al. 2021, Fagerli et al. 2024, Hattori et al. 2015, Hattori et al. 2016, Hattori et al. 2014a, Hattori et al. 2014b, Kimura et al. 2025, Kitamura et al. 2012, Kitamura et al. 2016, Lee et al. 2013, Lee et al. 2020, Lee et al. 2025, Mehla et al. 2017, Quintana et al. 2021, Quintana et al. 2018, Zhai et al. 2016

Figure 2. Summary of primary outcomes of surgical animal VCI models. Models include two-vessel occlusion (2-VO) and four-vessel occlusion (4-VO) transient global ischemia with reperfusion and bilateral common carotid artery occlusion (BCCAO), bilateral common carotid artery stenosis (BCAS), and bilateral common carotid artery gradual occlusion (BCCAGO) chronic global ischemia. Reductions in cerebral blood flow (CBF) vary from severe and temporary with reperfusion in 2- and 4-VO models to gradual and progressive in a BCCAGO model. White matter (WM) lesions, identified via histology, and WM hyperintensities, visualized via MRI, are reported for each model. Neurotransmitter and metabolic marker alterations are presented. Finally, cognitive, behavioral, and neuromuscular deficits are identified for each.

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3. Limitations Within the Field

Given the limited WM density in lissencephalic rodent models, the necessity for large animal models with improved clinical translatability is increasingly apparent [28,70,216,217]. Due to the size and simplicity of the rodent brain, deep WM lesions, and CBF are challenging to evaluate and do not fully recapitulate clinical pathology [217,218]. Additionally, though the rodent model is economically attractive and easily replicated, the lissencephalic rodent brain lacks the intricate cortical folding and corresponding WM vulnerability characteristic of gyrencephalic brains, reducing translatability to clinical disease. The lissencephalic rodent brain limits CBF exploration as compared to the gyrencephalic brain due to its lack of gyri folds, significant decrease in WM concentration, and lack of deep WM. The areas of greatest WM density in the rodent brain are the corpus callosum, internal/external capsules, and optic chiasm, which function as the regions of interest most often evaluated for WM injury and degradation [70]. The limited evidence of gross WM changes sub-optimally recapitulates injury to deep cortical WM noted in human pathology [219], though many models effectively elicit WM rarefaction as a substantial building block for pathophysiological understanding. Given the intricate molecular mechanisms underlying VCI development and progression, a multifaceted approach will be a necessary strategy in generating future translatable models development, preclinical and clinical trial optimization, and reliable novel biomarker identification for vascular cognitive disease.

In clinical evaluation, MRI is frequently used to establish baseline and pathologic deviations in CBF. Susceptibility-weighted imaging (SWI) identifies cortical and subcortical hemorrhage while T1-weighted imaging detects atrophy patterns. Fluid-attenuated inversion recovery imaging (FLAIR) is best utilized to demonstrate WM hyperintensities and identify deep periventricular or subcortical WM lesions [220]. MRI is not an overtly practical radiological imaging approach in rodent models, as resolution issues and artifact frequency are common challenges due to small brain size [218]. Rodent models primarily employ laser speckle imaging and laser doppler flowmetry to evaluate CBF but must rely more heavily on histology for WM changes. This is a major consideration as repeated measures cannot be performed on individual animals longitudinally over disease progression , thus preventing researchers from identifying potential diagnostic biomarkers. Functional MRI (fMRI) is a clinical MRI technique used to image blood flow and oxygen perfusion and is generally performed on conscious patients. However, due to the limitations of animal models, fMRI is difficult to perform in a directly translatable manner to clinical patients. Yet, modern use of large animal models has made it possible to evaluate resting-state fMRI changes in both healthy brains and injured brains in vitro, longitudinally [221–223]. Furthermore, the small rodent brain size requires field strength of approximately 4.7-11.7T versus the standard clinical 1.5-3T, thus generating a higher incidence of image artifact and noise [218]. Limited animal studies have demonstrated substantial subcortical CBF reductions using ASL, providing compelling evidence that MRI-based techniques offer a more reliable and precise representation of CCH-induced WM injury. The distinction in these WM populations must be made when considering the efficacy of CBF reduction in animal models, particularly those in which subcortical structures are challenging to image due to small brain size and low architectural complexity in rodents.

Current clinical assessment of VCI-associated pathophysiology in human medicine relies more heavily on the neuropsychological evaluation of executive function, attention, memory, language, and visuo-spatial function than imaging mechanisms, thus necessitating an animal model that can replicate functional and cognitive deficits and confirm histological correlations [224,225]. When subjected to various executive skills tests, patients with vascular dementia are found to have profound reductions in executive function with a strong correlation between advanced neuropsychological symptoms and reduced daily independence [226]. Functional outcomes are cornerstones to establishing and improving human quality of life following the onset of AD, vascular dementia, or post-ischemic small vessel disease. Establishing baseline functional outcomes from which subsequent treatment targets or prophylactic treatments can be developed will be critical for improving VCI prognosis.

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VCI animal models have been successful in recapitulating pathophysiology associated with clinical dementia at acute and chronic timepoints relative to study duration. Older rodents have been used in some studies, but baseline cognitive errors are typically elevated, making it challenging to extrapolate significant data [89,121,227,228]. Additionally, the lack of chronic studies limits the evaluation of disease progression. Rodent VCI models consistently demonstrate a natural CBF return to baseline between acute and chronic (14-30 days) timepoints [28,144,146,225]. Most models conclude 30 days post-procedure, at which point moderate CBF restoration is noted. Chronic models (>6 months) better replicate human pathophysiology by noting persistent CBF reductions and linearly related frontal cortex lesions, hippocampal atrophy, and cognitive deficits [22]. Future studies should emphasize evaluation of chronic cerebral hypoperfusion to recapitulate long-term disease progression in clinical settings.

4. Conclusions

As emphasized in this review, treatments and prophylactic therapies have been difficult to develop due to the complex VCI heterogeneity and its deleterious progression from initial onset. With no perfect model to recapitulate human VCI, model selection has proven pivotal for desired disease outcomes and intended investigation. Existing VCI models, however, do collectively present multiple methodologies of vascular impairment with structural and functional changes resultant from acute and chronic cerebral hypoperfusion. While each VCI model has unique advantages and limitations, the broader results display reductions in CBF, neuronal and WM degradation and loss, elevated inflammation markers, and behavioral and functional progressive decline. As the incidence of AD, VCI, and other spectral dementia pathologies continue to rise, there is a proportionally urgent need to investigate underlying mechanisms and pursue novel therapies.

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Abbreviations

The following abbreviations are used in this manuscript:

VCI	Vascular cognitive impairment
AD	Alzheimer's Disease
WM	White matter
CCH	Chronic cerebral hypoperfusion
CBF	Cerebral blood flow
2-VO	Two-vessel occlusion
4-VO	Four-vessel occlusion
BCCAO	Bilateral common carotid artery occlusion
BCAS	Bilateral common carotid artery stenosis
BCCAGO	Bilateral common carotid artery gradual occlusion
BBB	Blood brain barrier
MRI	Magnetic resonance imaging
T2W	T2-weighted
ADC	Apparent diffusion coefficient

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ASL	Arterial spin labeling
ChAT	Choline acetyltransferase

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