

● REVIEW

Large animal ischemic stroke models: replicating human stroke pathophysiology

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Funding: This work was supported by the National Institutes of Health, National Institute of Neurological Disorders and Stroke, No. R01NS093314.

Abstract

The high morbidity and mortality rate of ischemic stroke in humans has led to the development of numerous animal models that replicate human stroke to further understand the underlying pathophysiology and to explore potential therapeutic interventions. Although promising therapeutics have been identified using these animal models, with most undergoing significant testing in rodent models, the vast majority of these interventions have failed in human clinical trials. This failure of preclinical translation highlights the critical need for better therapeutic assessment in more clinically relevant ischemic stroke animal models. Large animal models such as non-human primates, sheep, pigs, and dogs are likely more predictive of human responses and outcomes due to brain anatomy and physiology that are more similar to humans—potentially making large animal testing a key step in the stroke therapy translational pipeline. The objective of this review is to highlight key characteristics that potentially make these gyrencephalic, large animal ischemic stroke models more predictive by comparing pathophysiological responses, tissue-level changes, and model limitations.

Key Words: brain ischemia; clinical translation; gyrencephalic; large animal model; magnetic resonance imaging; stroke

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doi: 10.4103/1673-5374.274324

Received: September 28, 2019

Peer review started: September 30, 2019

Accepted: November 4, 2019

Published online: January 28, 2020

Introduction

Resulting in approximately 142,000 deaths a year, stroke ranks 5th among all causes of death in the United States (Benjamin et al., 2019). Although the age-adjusted mortality rates for stroke decreased between 1990 and 2015, the absolute number of people who have strokes annually have increased worldwide (Benjamin et al., 2019). Given the high morbidity and mortality of stroke, animal models have been developed over the last four decades to replicate various aspects of human stroke to further understand underlying pathophysiological responses and explore potential treatments. Ischemic stroke caused by a blockage in the brain vasculature leading to brain ischemia is the most common type of stroke, accounting for 85% of all clinical cases (Mackay et al., 2004).

Due to ischemic stroke prevalence, a number of rodent ischemic stroke models (e.g., permanent middle cerebral artery occlusion and thromboembolic models) have been developed. Although current rodent models offer many advantages including low cost, well-characterized physiological responses, and the ability to investigate genetic manipulations and co-morbidities (e.g., diabetes, hypertension), the number of failed human clinical trials suggests additional testing in translational ischemic stroke models, more representative of the human condition, are needed for the assessment of novel therapies (Perel et al., 2007; Hossmann, 2009; Sicard and Fisher, 2009). Stroke Therapy Academic Industry Roundtable meetings of leading stroke experts have recommended that after sufficient evidence of therapeutic efficacy

has been collected in rodent models, large animal models of stroke should be used to increase clinical predictive value (Fisher and Stroke Therapy Academic Industry, 2003; Fisher et al., 2007, 2009). The use of an intermediate species may enhance successful translation given similarities in neuro-anatomical structures and clinical hallmarks relative to humans (**Figure 1**).

In order to advance our current understanding of human stroke pathophysiology and to develop novel therapies and devices, numerous pre-clinical animal models are widely employed. In this review, we will compare relevant brain anatomical and physiological characteristics between humans, non-human primates (NHPs), sheep, pigs, and dogs as well as consequential neurologic and motor function deficits post-stroke. Clinically relevant magnetic resonance-based outcomes will also be evaluated in these large animal models to assess tissue-level changes across acute and chronic time points (**Figure 2**). Finally, clinical translatability and experimental practicality will also be considered.

Search Strategy and Selection Criteria

The articles in this review were retrieved using the following electronic databases: PubMed, MEDLINE, and Google Scholar. The search was limited to articles published between July 7, 1953 and July 25, 2019. Search terms were identified in the title, abstract, and key words using the following search terms: stroke, ischemic infarct, stroke patients, middle cerebral artery occlusion, large animal model, non-hu-

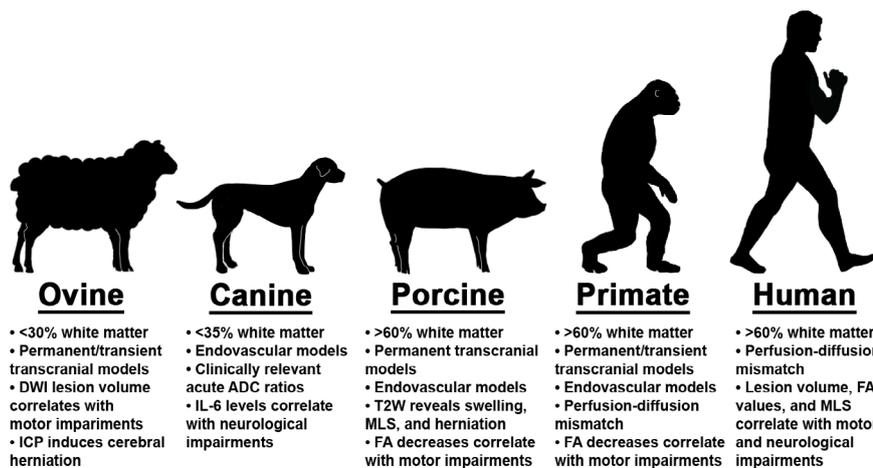


Figure 1 Major large animal models utilized to evaluate human ischemic stroke pathophysiology.

Inherent white matter composition, stroke type, surgical occlusion methods, and magnetic resonance assessments provide a platform to investigate human ischemic stroke pathophysiology and consequent functional outcomes. Collectively, these clinically relevant modalities enable researchers to characterize unique tissue-level and functional (e.g., sensorimotor) changes across acute and chronic time points. These tools possess indisputable value in identifying therapeutic targets and testing of novel treatments prior to clinical trials. ADC: Apparent diffusion coefficient; FA: fractional anisotropy; ICP: intracranial pressure; IL-6: interleukin 6; MLS: midline shift; T2W: T2 weighted.

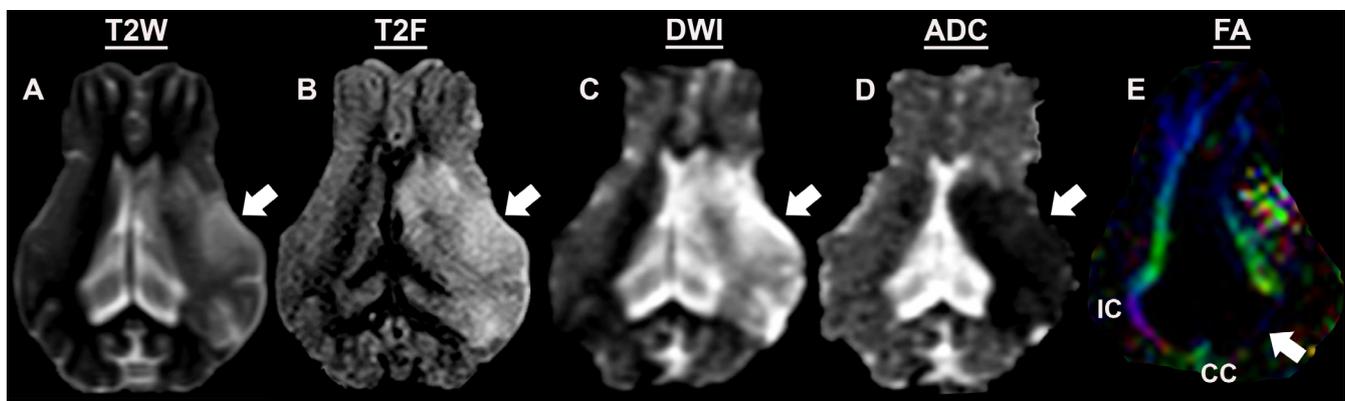


Figure 2 Magnetic resonance assessment of a preclinical pig ischemic stroke model 1-day post-middle cerebral artery occlusion.

Pathophysiological changes including increased hemispheric swelling, midline shift, and hyperintense lesion formation are observed in T2 weighted (T2W) (A) and T2 fluid-attenuated inversion recovery (T2F) (B) sequences. DWI (C) sequences showed hyperintense lesions indicative of territorial edematous injury, while corresponding hypointense lesions on ADC maps (D) confirmed restricted diffusion and cytotoxic edema. FA maps (E) revealed increased loss of WM integrity in the internal capsule (IC) and the corpus callosum (CC). ADC: Apparent diffusion coefficient; DWI: diffusion weighted imaging; FA: fractional anisotropy; WM: white matter.

man primates, sheep/ovine, pig/porcine/swine, dog/canine, magnetic resonance imaging, motor function, neurological score.

Large Animal Ischemic Stroke Models

Non-human primate ischemic stroke models

The use of gyrencephalic NHP species for translational stroke research is an attractive alternative due to their remarkable anatomical similarity to the human brain. NHPs have comparable complex cortical organization with deep white matter (WM) tracts, white (> 60%) and gray matter composition, and cerebral vasculature that closely resembles humans (**Figure 1**) (Cook and Tymianski, 2011). Furthermore, NHPs possess relatively thick cortices and numerous, high-velocity neurons, thus allotting for superior cognitive and behavioral processing capacities during neurobehavioral testing (Cook and Tymianski, 2012; Roth and Dicke, 2012). These favorable anatomical similarities have led to the development of several NHP ischemic stroke models.

Historically, the primary NHP stroke model utilized to investigate cerebral ischemia was the baboon permanent middle cerebral artery occlusion (MCAO) model (Spetzler et al., 1983; Nehls et al., 1986). This model resulted in key stroke

hallmarks such as ischemia, classical cytotoxic edema and lesioning of the brain. However, this model produces marked cerebral edema requiring prolonged intensive care of the animal and is associated with a high risk of mortality making it a challenging model to study. In addition, this permanent occlusion model did not allow for reperfusion, which is common in human patients, limiting its potential to assess key aspects of ischemic stroke like reperfusion injury. As a result, transient NHP models were developed in order to gain a better understanding of secondary reperfusion injury and successive microvasculature failure. Del Zoppo et al. (1986) describes a balloon transorbital reperfusion baboon model with increasing cortical lesion volumes observed between 10 days ($3.2 \pm 1.5 \text{ cm}^3$) and 14 days ($3.9 \pm 1.9 \text{ cm}^3$) post-stroke with functional deficits including contralateral hemiparesis, facial paresis, and mydriasis of variable degrees due to internal capsule, putamen, and caudate nucleus involvement. In addition, microvascular clip reperfusion baboon models exhibit lesion volumes (30% of the ipsilateral hemisphere) and progressive temporal evolution similar to humans as assessed by MRI diffusion weighted imaging (DWI) and T2 Weighted (T2W) structural sequences (Huang et al., 2000; D'Ambrosio et al., 2004; Giffard et al., 2005). Functional defi-

cits including hemiparesis of the contralateral arm and leg were thought to arise from the loss of the tissue integrity in the striato-capsular area with internal capsule and basal ganglia involvement. In the context of human ischemic stroke, these results possess important implications for researchers given that many human studies confirm this delayed evolution of ischemic areas with mean lesion volumes significantly ($P < 0.0001$) higher at 7 days compared to 1-day post-stroke in patients (Pantano et al., 1999; Saver, 2006). Moreover, most stroke patients also exhibit hemiparesis with correlative asymmetries in arm, leg, trunk, and face movements due to internal capsule, putamen, and basal ganglia involvement in the complex communication and feedback loops between the areas of the cerebral cortex and the brainstem (Ng et al., 2007; Patterson et al., 2008). Restoring functional deficits in stroke patients is critical for improvements in patient quality of life and is an important measure of a treatment's therapeutic potential in animal models (Sofuwa et al., 2005; Liao et al., 2008; Veerbeek et al., 2011).

Macaque reperfusion models generated by transorbital and pterional craniotomy approaches have been characterized with both methods of cerebrovascular access while producing representative ischemic lesions. In addition to modeling the structural damage of stroke, these models mirror functional deficits including reduced strength and skilled movement of upper limbs with the loss or disruption of motor and sensory cortices, similar to the human condition (Nakayama et al., 1994; Cirstea and Levin, 2000; Nudo et al., 2001). Chin et al. (2010) reported transient decreases in MRI WM fractional anisotropy (FA) values, suggesting loss of integrity of the ipsilateral motor pathways at the dorsal region of the internal capsule at 7 days post-stroke. This correlated with deficits in motor function including paralysis and weakness in upper and lower limbs as well as incoordination. However, motor function recovered to baseline at 6 weeks post-stroke. This gradual motor recovery observed in macaques has also been reported in chronic stroke patients where gradual motor recovery is also observed and correlates with WM FA value changes (Pierpaoli et al., 2001; Biesbroek et al., 2017). West et al. (2009) characterized varying durations of microvascular clip occlusion and consequent mean lesion volumes at 45 minutes ($1.983 \pm 2.51 \text{ cm}^3$), 60 minutes ($2.381 \pm 6.54 \text{ cm}^3$), and 90 minutes ($4.707 \pm 12.7 \text{ cm}^3$) as determined by T2W imaging in macaques (West et al., 2009). Consequent ischemia encompassed portions of the frontal and parietal lobes, insular motor cortex, and cingulate cortex with the severity of hemiparesis in the extremities and face consistent with clinical stroke patients diagnosed with damaged neuronal motor cortex circuitries (Traversa et al., 2000; West et al., 2009). In a similar study by Murphy et al. (2008) a 90-minute occlusion produced infarcts extending from the caudate nucleus and putamen (basal ganglia), external capsule, and adjacent subcortical WM in macaques. Multiple human clinical trials and large cohort studies have characterized these frontotemporal abnormalities with most involving both basal ganglia and WM compartments (Saver, 2006). Final patient volumes in clinical trials range from 19

to 138 cm^3 (3.33–24.17% of the ipsilateral hemisphere), thus suggesting 45 minutes ($19.0 \pm 0.98\%$ of the ipsilateral hemisphere) and 60 minutes ($22.1 \pm 4.6\%$ of clip application) are more clinically relevant macaque models of ischemic stroke as compared to 90 minutes ($44.4 \pm 4.0\%$ of temporary occlusion) (Saver, 2006).

Endovascular occlusion using an autologous blood clot, coil, or surgical suture has also been widely developed in macaques to induce focal ischemia. Advantages of these methods include 1) they are minimally invasive and avoid the need for enucleation and its associated loss of vision and impacts on neurobehavioral assessments, 2) they are capable of achieving reperfusion, and 3) they directly affect the intracranial vessels, thus avoiding surgically induced damage to the endocranium and intracranial environment. Autologous blood clot models have induced ischemic lesions ($28.3 \pm 12.4\%$ of the ipsilateral hemisphere) affecting the caudate, globus pallidus, putamen, internal capsule, claustrum, and insular cortex (Hillet et al., 1955; Kito et al., 2001). Clinical signs compatible with selective occlusion of these middle cerebral artery (MCA) territories in humans were also observed in macaques exhibiting contralateral facial sensation, pinna and pain reflexes, and severe paralysis of contralateral hands and legs. Furthermore, significant correlations between macaque lesion volumes and total neurologic deficit scores were observed, with similar correlations commonly seen between acute ischemic stroke patient lesion volumes and the National Institutes of Health Stroke Scale neurological scores (Kito et al., 2001; Furlanis et al., 2018).

The ischemic penumbra is classically defined as potentially salvageable hypoperfused tissue and is the difference between the perfusion weighted imaging (PWI) lesion volume and the DWI lesion volume in stroked tissue (Astrup et al., 1981; Kakuda et al., 2008). This PWI/DWI mismatch is a key characteristic in both NHP and human stroke pathology and has prompted alterations in therapeutic targets and treatment windows (Hossmann, 1994; Wey et al., 2011). Alternative penumbra imaging concepts more technologically available have also been recently developed using diffusion tensor imaging (DTI) and associated FA values. For example, in a recent study by Neal et al. (2015), they demonstrated that patients with acute ischemic stroke (< 6 hours) exhibited decreased FA values in regions of ischemic core, yet increased FA values in hypoperfused penumbra tissues. This trend suggests DTI and FA related changes in humans could be used to differentiate penumbra and ischemic core in addition to currently used PWI/DWI comparisons. Comparatively, NHP coil endovascular occlusion revealed a PWI/DTI mismatch with PWI lesion volumes being larger than DTI abnormalities at 1 hour post-stroke with the difference being penumbra (Guo et al., 2011). A similar NHP suture model also identified penumbra evolution as detected by DWI and corresponding apparent diffusion coefficient (ADC) maps followed by T2W sequences (Rodriguez-Mercado et al., 2012). Liu et al. (2007) provided further evidence that the evolution of stroke in macaques is closer to what has been observed in humans than in rodent models by comparing

ADC and FA maps with T2W and T2FLAIR sequences to establish the temporal profile of diffusion changes and to determine endpoint lesion volumes in permanent and transient MCAO models. In human studies, the mean time of pseudo-normalized ADC (i.e., return to an apparently normal ADC value) was ~10–14 days, while in rodent studies a pseudo-normalized ADC was often found much earlier at ~1–4 days post-stroke, likely due to inherent differences in cerebrovascular collateralization and cytoarchitecture (Eastwood et al., 2003; Munoz et al., 2004; Liu et al., 2007). Comparatively, NHP ADC pseudonormalized at ~8 days in lissencephalic marmosets and ~10 days in gyrencephalic macaques, providing further support for the use of gyrencephalic NHP species that more adequately replicate human penumbra evolution post-stroke (Liu et al., 2007; Bihelet et al., 2010). Wey et al. (2011a, b) implemented arterial spin labeling to characterize the spatial-temporal characteristics associated with perfusion-diffusion mismatch and provided evidence that reperfusion salvaged damaged penumbra tissue in a transient baboon model. In humans, this perfusion-diffusion mismatch is often detected for up to 12 hours post-stroke with the frequency of detection decreasing over time (Darby et al., 1999; Shen et al., 2003; Zhang et al., 2015b). Comparatively, this mismatch volume has shown to be detectable for up to 6 hours in both baboons and macaques, whereas it is only detectable for up to 3 hours post-stroke in rodent models (e.g., intraluminal reperfusion models). The similarities in the manifestation, evolution and detection of the salvageable penumbra region between humans and primates provides researchers with valuable information on ischemic stroke pathophysiological changes and the ability to better assess drugs targeting the salvageable penumbra tissue (Astrup et al., 1981; Warach et al., 1996).

Non-human primate ischemic stroke model considerations

Despite the translational potential of primate models, there are a number of important practical and scientific disadvantages that have limited the use of these models. Baboons exhibit a network of arteries that communicate between the bilateral anterior cerebral arteries (ACAs) rather than the single vessel found in humans, which may influence Circle of Willis collateralization (Kapoor et al., 2003). Additionally, some NHP species, sheep, and pigs demonstrate complete anterior communicating artery (CoA) hypoplasia, which may result in poor outcomes due to decreased cerebral blood flow (Combs et al., 1990; Sorby-Adams et al., 2018). Baboon MCAO models are associated with high premature mortality rates and prolonged intensive care (Nehls et al., 1986; Huang et al., 2000; D'Ambrosio et al., 2004). Some permanent and transient occlusion methods in baboons and macaques require enucleation for transorbital access to the MCA and the ACA, thus limiting neurobehavioral assessments due to binocular vision loss (Nehls et al., 1986; Tagaya et al., 1997; Mack et al., 2003; D'Ambrosio et al., 2004). Cynomolgus and rhesus macaque endovascular induction methods require substantial technological and surgical skill and may produce

unreliable anterior circulation stroke patterns (Kito et al., 2001; Kuge et al., 2001; de Crespiigny et al., 2005; Wu et al., 2016). Reperfusion in autologous blood clot models is difficult to control, while microcatheter embolization methods utilizing metal coils or guide wires prohibits the use of MRI prior to reperfusion. The extensive limitations of cost, housing facilities, veterinary care, and ethical challenges associated with NHP models warrant further investigation of alternative large animal species for modeling ischemic stroke.

Ovine ischemic stroke models

Sheep are a highly promising surrogate for modeling human stroke due to inherent anatomical similarities including gyrencephalic cerebral structure with dense WM tracts (Bataille et al., 2007). A strong fibrous dura mater and tentorium cerebelli also play a significant role in modeling human ischemic stroke by confining post-stroke increases in intracranial pressure (ICP) to the supratentorial compartment (Klintworth, 1968; Gabrielian et al., 2011). Comparatively, rodents have a weak vestigial connective tissue membrane that enables distribution of ICP into other compartments. Increases in ICP in humans and large gyrencephalic animals post-stroke are therefore more significant and more common than in rodents and often leads to loss of consciousness, cerebral herniation, and premature death. Sheep cerebrovasculature also facilitates the development of sheep stroke models as the intradural internal carotid artery (ICA) supplies blood to a majority of the supratentorial structures and, like humans, the terminal intradural ICA bifurcates to the ACA and MCA (Ashwini, 2008). Despite these similarities, sheep possess a reticulated arterial anastomosis between the maxillary and internal carotids known as the rete mirabile (Daniel 1953; Hoffmann et al., 2014). This capillary network at the branch of the common carotid artery renders endovascular models of cerebral ischemia virtually impossible due to the minute diameter of arterial vessels, thus transcranial stroke induction approaches are typically required.

Permanent occlusion in sheep via frontotemporal craniectomy boasts a number of advantages including preservation of post-operative binocular vision, unlike NHP transorbital models, as well as lesion reproducibility due to the length of the ICA which aids in proximal MCA accessibility (Kapoor et al., 2003). Boltze et al. (2008) reported DWI-based lesion volumes could be titrated, with complete MCAO lesion volumes being significantly greater than 2-branch and 1-branch-MCAO lesion volumes (16.3 ± 5.2 vs. 8.7 ± 3.9 vs. 5.6 ± 3.6 cm³, respectively) at 1-day post-stroke. These significant differences in lesion volumes were maintained between subgroups up to 42 days post-stroke. Lesion volume was found to be correlated with functional outcomes based on a novel sheep-specific neurobehavioral score system with important metrics including unconsciousness, ataxia, fetlock flexion weakness, delayed hemistanding, circling behaviors, and impaired hopping reactions. Comparatively, complete proximal MCA occlusion in humans resulted in similar motor and somatosensory deficits including ataxia and hemiparesis of contralateral upper and lower extremities.

ties as well as loss of consciousness due to significant cerebral edema and swelling (Battey et al., 2014). Furthermore, T2W sequences in sheep revealed significantly higher atrophy ratios for the complete MCAO group compared to the 2-branch-MCAO group, whereas 1-branch-MCAO resulted in significantly less atrophy ratios compared with 2-branch-MCAO 42 days post-stroke (Boltze et al., 2008). Although this model maintains clinically relevant tissue and functional-level deficits at acute and chronic time points, it also exhibits unrealistic survivability rates (100%) post-stroke. Researchers believe these survival rates are due to reduced ICP at the craniectomy site and is therefore a notable limitation of the model.

To address the translational limitations of the permanent sheep occlusion model, Wells et al. later developed a transient sheep occlusion model and performed a head to head comparison to more accurately assess intracranial dynamics and reperfusion mechanism differences between these models (Wells et al., 2012, 2015). As expected, lesion volumes were greater in permanent occlusion sheep compared to transient occlusion sheep (27.4–28.8% vs. 7.9–14.6% of the ipsilateral hemisphere, respectively) with ischemia affecting both cortical and subcortical structures in both models. DWI deficits were also greater in permanent occlusion sheep compared to transient occlusion sheep ($25.4 \pm 6.8\%$ vs. $10.7 \pm 3.9\%$, respectively) with restricted diffusion reported throughout the entire right MCA territory and basal ganglia in permanent occlusion sheep and throughout the right caudate head and genu of the internal capsule in transient occlusion sheep. T2W sequences revealed similar model differences in edema volume ($25.0 \pm 4.9\%$ vs. $5.4 \pm 4.1\%$ of the ipsilateral hemisphere) resulting in increasing midline shift (MLS) (3.3 ± 0.6 mm vs. 1.0 ± 0.8 mm). Sorby-Adams et al. (2019) recently reported significantly elevated ICP levels in excess of 20 mmHg at 5–6 days post-transient MCAO in sheep. These findings are comparable to human patients in which cerebral edema and ICP peak around 3–5 days following initial ischemic insult (Hewitt, 2012). Clinically, ICP readings > 20 mmHg warrant treatment intervention as persistently elevated ICP following MCA infarction is commonly associated with rapid neurological deterioration (Treadwell and Thanvi, 2010; Lavinio and Menon, 2011; Battey et al., 2014). Death is common in the 78% of patients that experience herniation and consequent brainstem compression due to ICP (Hacke et al., 1996; Wang et al., 2011). The sequela of herniation and comparative mortality rates observed in the transient sheep model further supports the use of this clinically relevant large animal model in order to study ICP related pathology and decompressive therapies.

Ovine ischemic stroke model considerations

Arguably the most notable disadvantage of sheep models is the rete mirabile. This dense network of small diameter arteries renders endovascular methods of ischemic induction unfeasible, thus necessitating rather complex transcranial surgical approaches to induce MCAO. Transcranial approaches disturb endocranium dynamics and may lead

to hematomas or hemorrhagic transformation as seen in approximately ~12% patients with MCA infarctions that undergo decompressive craniectomies (Kenning et al., 2012; Lee et al., 2012). Furthermore, surgical craniectomy permits the loss of cerebrospinal fluid (CSF) upon dural excision and minimizes the pathological development of elevated ICP following MCA occlusion (Boltze et al., 2008). Common assessments of patient injury severity and prognosis in clinical settings are often based on neurological symptoms including pupillary dilation, anisocoria, consciousness, and paralysis which are caused by excessive ICP (Chen et al., 2011). Without representative increases in ICP, craniectomy sheep occlusion models display notable alterations in stroke pathophysiology, thus decreasing this model's translational potential. Furthermore, with < 30% WM, sensorimotor impairments commonly associated with WM injuries in stroke patients may not be fully replicated in sheep models (**Figure 1**) (Sahin, 2001; Nitzsche et al., 2015; Wang et al., 2016). Perhaps similarities in other critical brain characteristics overcome this limitation, yet this remains to be determined.

Porcine ischemic stroke models

Pigs possess notable translational advantages due to inherent neuroanatomical similarities including gyrification, large intracranial vessel diameter, and a high white-to-gray matter ratio (Gralla et al., 2006; Kobayashi et al., 2012). Proportionally comparable cerebral volumes between humans and pigs (1273.6 cm³ for men and 1131.1 cm³ for women vs. 111.09 cm³ for males and 103.15 cm³ for females) allows for a more direct assessment of therapeutic dosing in a preclinical model (Allen et al., 2002; Conrad et al., 2012). In terms of cytoarchitecture, human and pig brains are composed of > 60% WM (**Figure 1**) (Tanaka et al., 2008; Nakamura et al., 2009). These attributes are critically important as WM and gray matter demonstrate different metabolic needs due to neuroanatomical differences. Specifically, neuron-rich gray matter requires 2.5 times more ATP and consequently 3–5 times more vascularization than WM (Borowsky and Collins, 1989; Nonaka et al., 2003; Peters et al., 2004). The increased vascularization of gray matter permits some protection following ischemic events, however the limited collateralization of WM leaves these tissues particularly susceptible to ischemic insult and is a critical factor to consider when modeling human ischemic stroke. Experimental pig stroke models have also been characterized with human MRI modalities and may help provide critical insight into the refinement of acute stroke detection (**Figure 2**). Lastly, high purchase and housing costs as well as ethical challenges associated with other large animal models are less pronounced in pigs making them an attractive alternative (Kobayashi et al., 2012).

Similar to sheep, the rete mirabile network in pigs makes endovascular methods of MCA occlusion challenging (Stroke Therapy Academic Industry, 1999; Sakoh et al., 2000b; Watanabe et al., 2007; Ashwini, 2008). Watanabe et al. (2007) developed a permanent pig MCAO model in which the proximal MCA was occluded via permanent electrocautery utilizing a transorbital approach. Although transorbital in-

duction has been well characterized in NHP models as an efficient method of inducing focal cortical infarction, DWI analysis in pigs revealed varying lesion volumes in relation to the magnitude of residual flow following MCAO (Sakoh et al., 2000a; Watanabe et al., 2001, 2007). Subsequent loss of binocular vision and limited neurobehavioral and gait assessments were additional limitations (Sakoh et al., 2000b). Comparatively, frontotemporal MCAO approaches avoid the need for enucleation and intraorbital decompression making it a favorable alternative over transorbital approaches (Imai et al., 2006; Platt et al., 2014; Baker et al., 2017; Webb et al., 2018). This model provides increased visibility of the MCA and its associated branches, thus resulting in repeatable ischemic injury with consistent lesion volumes. Platt et al. (2014) showed pigs, like humans, exhibit a standard evolution of ischemic injury with cytotoxic edema primarily observed as hypointense ADC abnormalities followed by delayed vasogenic edema (Ho et al., 2012). Additionally, as pig cerebrums are approximately 7.5 times smaller than humans, the West Laboratory has recently confirmed pig DWI lesion volumes ($9.91 \pm 3.14 \text{ cm}^3$; unpublished data) closely replicate patient DWI lesion volume thresholds of 72 cm^3 , which frequently correspond to major cerebral artery occlusions and poor neurological outcome (Sanak et al., 2006; Gonzalez, 2012).

T2W sequences in the pig MCAO model revealed acute hemispheric swelling ($126.8 \pm 3.4\%$ change from contralateral hemisphere), pronounced MLS, and cerebellar herniation with functional deficits in gait and behavior performance as well as premature death (Webb et al., 2018). T2W visualized hemispheric swelling and MLS in patients is also considered a robust predictor of cerebral herniations and patient death as rapid neurological deterioration often leads to 60–80% 30-day patient mortality rates (Ropper, 1986; Hacke et al., 1996; Berrouschot et al., 1998; Walberer et al., 2007; Treadwell and Thanvi, 2010). Hemispheric swelling often instigates herniation leading to abnormal protrusion into adjacent neural structures or through rigid intracranial barriers (i.e., the foramen magnum) (Klintworth 1968; Kotwica et al., 1991; Gabrielian et al., 2013). The tentorium cerebelli in humans and large animal species is relatively strong, which limits and alters the displacement of the brain post-stroke. Comparatively, rodents possess a weak tentorium cerebelli that permit the displacement of the brain. This results in inconsistencies between rodent and human swelling responses post-stroke. DTI sequences have revealed permanent pig MCAO also replicates patient reductions in WM integrity of the internal capsule and corpus callosum at acute and chronic time points (Baker et al., 2017; Webb et al., 2018). These reductions in WM integrity were coupled with deteriorations in pig spatiotemporal and relative gait pressure measurements including velocity, cadence, swing percent of cycle, stride length, cycle time, and mean pressure. Likewise, these deficits correlate with contralateral deteriorations in patient motor function, as studies utilizing Functional Ambulatory Categories found patients with internal capsule lesions exhibited persistent (> 6 months) motor deficits and required aids for balance and support during ambulation (Baltan et al., 2008;

Srikanth et al., 2009; Ahmad et al., 2015; Lee et al., 2017). Understanding how brain ischemia leads to WM changes and consequent motor deficits, preferably in models with comparable WM content (> 60%), is a research priority that will help advance strategies for WM repair and regeneration.

Consequential damage to the dura and disrupted ICP evolution in the pig craniectomy models has led to the development of an endovascular pig model. Cui et al. (2013) established an endovascular model of focal ischemic stroke in miniature pigs in which sodium alginate microspheres, a biodegradable material, were injected through the femoral artery to embolize the rete mirabile as confirmed by angiographic and DWI analysis. Signal abnormalities on T2W sequences revealed lesion volumes encompassing approximately 30% of the ipsilateral hemisphere with notable ischemia in the temporal and parietal lobes and the basal ganglia. Infarction in these regions prompted mild hemiplegia and associated ambulation impairments in balance and coordination as early as 12 hours post-stroke. Interestingly, stroke patients with confined basal ganglia and internal capsule injury exhibit persistently impaired balance and ambulation performance as well (Miyai et al., 1997). These observed motor memory deficits are likely due to persistent dysfunction in the cortico-basal ganglia-thalamo-cortical loop, an intricate neural circuit system responsible for facilitating voluntary movements while simultaneously inhibiting competing or interfering movements (Boyd et al., 2009; Simonyan, 2019).

Porcine ischemic stroke model considerations

Like the sheep, the rete mirabile necessitates transcranial approaches that damage the cranium and dura and result in uncharacteristic intracranial dynamics and cerebrovascular pathophysiological changes post-stroke (Imai et al., 2006). Although an endovascular occlusion method has been described, minimal sample size, short observation windows, and occlusion of the anatomical anastomosis the rete mirabile (a more distal vasculature structure), limits the clinical translatability of this model. Furthermore, the posterior CoA in the Circle of Willis in both pigs and sheep is comparable to the diameter of the anterior cerebral artery whereas in humans the posterior CoA is approximately half the diameter of the anterior cerebral artery. (Ashwini, 2008; Deepthi, 2016). These variations in vessel diameter are an important consideration when modeling ischemic stroke as equal blood volume flows through both divisions of internal carotid artery in animals whereas in humans the blood flow through the posterior CoA is reduced, thus impacting collateral flow within the Circle of Willis. Pig plasminogen also displays high resistance to tPA activation due to unique plasminogen-streptokinase interactions (Yakovlev et al., 1995; Flight et al., 2006). As a result, investigation of combination therapies in conjunction with tPA are hindered, even if a clot model were available.

Canine ischemic stroke models

Similar to previously discussed large animal models, dogs

demonstrate conserved gyrencephalic structure, well-established WM tracts, and large cerebrovascular diameter (Traystman, 2003). Additionally, unlike sheep and pigs, dogs lack a rete mirabile. This anatomical similarity to humans favors endovascular approaches of stroke induction and is one notable translational advantage of dog models (Gralla et al., 2006; Howells et al., 2010). Permittable endovascular access avoids the need for enucleation or invasive transcranial procedures to access the MCA thus preserving dura, cerebral spinal fluid volumes, and post-stroke ICP. The use of dogs also minimizes economic, housing, and handling difficulties commonly associated with NHP use, however ethical concerns remain a notable consideration (Hillock, 2006).

First described by Hill et al. (1955) several studies have since reported on various endovascular methods for inducing MCAO in dog models (Shaibaniet al., 2006; Rink et al., 2008; Christoforidis et al., 2011). Permanent MCA, achieved via ICA injection of synthetic emboli, induced lesion volumes $32.13 \pm 11.98\%$ in the basal ganglia, left ventral cortex, left ventrolateral cortex, and left cortex of the cerebrum with swelling, MLS, and mass effect observed via T1W sequences (Kang et al., 2007). Kang et al. (2009) later reported a mean ADC ratio (0.77 ± 0.08) that closely replicated human ADC ratios (0.5–0.8) at acute post-stroke time points (van Everdingen et al., 1998; Lee et al., 2005). Accumulation of cytotoxic and vasogenic edema were well-preserved within this model, thus presenting a significant advantage over photothrombotic rodent models (Carmichael, 2005; Kang et al., 2007, 2009; Macrae, 2011). Interestingly, dog CSF concentration of interleukin-6 (IL-6) positively correlated with the severity of neurological deterioration and death. This correlation has also been observed in several human stroke studies in which elevated CSF levels of IL-6 were found to positively correlate with ischemic lesion volumes and poor functional outcome (Tarkowski et al., 1995, 1997). As CSF IL-6, unlike serum IL-6, maintains significant predicative value in both dog and human stroke, further examination of this potential biomarker may help identify at-risk patients prior to onset of severe neurological symptoms and death.

Endovascular occlusion can also be achieved via coil placement in dogs through the vertebral artery (VA) in order to control for the variable intricacies of the ICA as previously mentioned (Atchaneeyasakul et al., 2016). Coil models offer a number of translational advantages as angiographic guidance in dogs is significantly superior when compared to rodent models where the relative size of the cranial arteries limits procedural evaluation and confirmation of occlusion (Flecknell et al., 2009). This method utilizes comprehensive imaging techniques to precisely position the coil encased within a microcatheter through the proximal M1 until appropriate permanent or transient occlusion of the MCA is achieved. Although the use of imaging guidance requires a complex understanding of dog cerebrovasculature, it enables specificity in coil placement that cannot be achieved by emboli injection via ICA. This yields definite and reproducible dog ischemic lesions of approximately $9.81\text{--}20.58\text{ cm}^3$ ($30.9 \pm 2.1\%$ and $31.2 \pm 4.3\%$, as reviewed by two independent

observers) as determined by T2 structural sequences 1-day post-stroke (Rink et al., 2008, 2011). DTI fiber tract projections from the region of the internal capsule to the corona radiata were dramatically reorganized with impaired connectivity in stroke dogs (Rink et al., 2011). These corticospinal and corticobulbar tracts that descend through the corona radiata and posterior limbs of the internal capsule mainly originate in the primary motor cortex in humans and play an important role in recovery of motor deficits (Higano et al., 2001; Kunimatsu et al., 2003). These anatomical similarities may provide important insights into the WM responses to hypoxia as well as necessary therapeutic measures to induce recovery of these WM structures.

The distal injection of autologous clots through the ICA accurately mimics human ischemia and is amenable to studies investigating the efficacy of novel thrombolytic therapies or thrombectomy devices. Despite clinical applicability, this model induces inconsistent lesion distribution as the precise site of occlusion cannot be controlled due to individual vascular variability, particularly of the ICA (Liu et al., 2012). Variations in emboli size have also contributed to variations in lesion volumes. Liu et al. (2012) reported clots 1.7 mm in diameter resulted in small, variable lacunar infarcts of $0.148 \pm 0.133\text{ cm}^3$ at 6 hours (DWI), $0.150 \pm 0.154\text{ cm}^3$ at 24 hours (T2W), and $0.095 \pm 0.115\text{ cm}^3$ at 7 days post-stroke (T2W) affecting the internal capsule and caudate. Zu et al. (2013) reported clots 1.4–1.7 mm in diameter resulted in mean infarct volumes of $4.17 \pm 0.06\text{ cm}^3$ at 24 hours (T2W) and $3.27 \pm 0.062\text{ cm}^3$ at 7 days post-stroke (T2W) affecting the basal ganglia and cortex. Van der Bom et al. (2012) described larger clots of 2.33 mm in diameter that induced extremely variable infarct volumes 4 hours post-stroke (0.12 to 12.53 cm^3 , ADC). These discrepancies were suggested to be due to convoluted ICA and perfusion differentials from the extensive leptomeningeal collaterals and have contributed to heterogeneous strokes in dogs (Symon, 1960; Harris et al., 2009; Christoforidis et al., 2011).

In addition to MCAO models, vertebral artery occlusion (VAO) and basilar artery occlusion (BAO) models have also been developed. In VAO models, high vertebral artery blood pressure often prevents emboli from anchoring to the vessel wall, thus limiting experimental efficacy. To address this, a recent study utilized a preinstalled self-expanding thrombus filter in the delivery catheter to allow for successful implantation of emboli (Zhang et al., 2015a). Although further imaging and clinical outcome studies of this canine model are still needed, this model may be useful to evaluate novel endovascular therapy for acute VAO in humans. The BAO model comparatively is commonly used to test recanalization by intravenous versus intraarterial thrombolysis. Qureshi et al. (2004) reported significant lesion formation following autologous clot injection into the proximal portion of the basilar artery with intraarterial thrombolysis affording a recanalization rate similar to that of intravenous thrombolysis, but with a lower rate of intra-cerebral hemorrhage. The most relevant disadvantages of BAO models are the exaggerated neurological deficits, prolonged intensive care, and

premature mortality which limit longitudinal assessments of therapeutic efficacy, functional outcomes, and tissue recovery post-stroke.

Canine ischemic stroke model considerations

An appreciable concern in dog models is the low extent of WM (35%), similar to that observed in sheep (< 30%) (Figure 1) (Krafft et al., 2012). Limited WM in these models may hinder advancements in understanding WM pathophysiology and mechanisms involved in ischemic injury (Ahmad et al., 2015). Conversely, NHPs and pigs display comparable WM to humans (> 60%) that results in similar prognosis and motor function decline commonly associated with human WM hyperintensities post-stroke (DeBette and Markus, 2010). Occlusion of the MCA is primarily achieved via ICA access, yet this procedure requires great surgical skill due to the intracavernous connection between the torturous ICAs as well as the small diameter of microcatheter administration systems (Nanda and Getty, 1975; Rink et al., 2008). A number of dogs exhibit extensive leptomeningeal anastomoses branching from the posterior, middle, and anterior cerebral artery, potentiating variation in lesion volume due to differentials in collateralization (Symon, 1960). Variation in vascular diameter, organization and physiological responses such as vasospasms between dog breeds may also limit reproducibility and experimental outcomes especially as mongrel dogs are commonly used (Rink et al., 2008, 2011). In the endovascular coil model, Rink et al. (2011) reported the coil positioned to occlude the proximal MCA, ACA, and distal ICA resulted in premature mortality of ~38% of the dogs within 1-day post-stroke. These experimental challenges in combination with pronounced ethical complications, limit the widespread use of canine species.

Conclusion

The stroke field agrees that a therapeutic breakthrough will most likely require a multifaceted approach including innovations in clinical trial design, consideration of systemic biomarkers, and optimization of therapeutic dosing. Large animal ischemic stroke models are a key part of this approach providing more predictive models for identifying potential treatment targets and testing novel therapeutics. While rodent models provide invaluable insight into the initial characterization and screening of potential therapeutic interventions, the significant failures of novel pharmacological agents in clinical trials may be partly due to the use of animal models that do not fully reflect stroke pathophysiology as it occurs in humans. As highlighted throughout this review, NHP, ovine, porcine, and canine ischemic stroke models possess significant advantages including comparative brain anatomy, similar tissue-level and functional responses, and compatibility with clinically relevant MRI techniques. To further enhance the predictive power of these large animal models, advances need to be made to develop thromboembolic clot models that will more closely mimic patient vascular occlusion mechanisms, enable the study of reperfusion injury and

evaluate the effects of novel combined therapies with thrombolytic agents. These large animal models must be enlisted as an important step in the translational framework in order to successfully bridge the gap between preclinical basic studies and effective therapies in human patients.

Acknowledgments: *The authors would like to thank Dr. Kylee Duberstein, Dr. Holly Kinder, and Kelly Scheulin for their valuable editorial critiques of this review.*

Author contributions: *Both listed authors made a substantial contribution to the concept and interpretation of the literature; drafted the review; revised it critically for important intellectual content; and approved the version to be published.*

Conflicts of interest: *The authors declare no conflicts of interest.*

Financial support: *This work was supported by the National Institutes of Health, National Institute of Neurological Disorders and Stroke, No. R01NS093314.*

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