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Review

Large animal canine endovascular ischemic stroke models: A review

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ABSTRACT

Background: Stroke is one of the leading causes of death and long-term disability worldwide. Recent exciting developments in the field with endovascular treatments have shown excellent outcomes in acute ischemic stroke. Prior to translating these treatments to human populations, a large-animal ischemic stroke model is needed. With the advent of new technologies in digital subtraction angiography, less invasive endovascular stroke models have been developed. Canines have gyrencephalic brain similar to human brain and accessible neurovascular anatomy for stroke model creation. Canine stroke model can be widely utilized to understand the disease process of stroke and to develop novel treatment. Less invasive endovascular internal carotid emboli injection and coil embolization methods can be used to simulate transient or permanent middle cerebral artery occlusion. Major restriction includes the extensive collateral circulation of canine cerebral arteries that can limit the stroke size. Transient internal carotid artery occlusion can decrease collateral circulation and increase stroke size to some degree. Additional method of manipulating the extent of collateral circulation needs to be studied. Other types of canine stroke models, including vertebral artery occlusion and basilar artery occlusion, can also be accomplished by endovascular thrombi injection.

Conclusions: We extensively review the literature on endovascular technique of creating canine ischemic stroke models and their application in finding new therapies for ischemic stroke.

Contents

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ICA, internal carotid artery; ECA, external carotid artery; VA, vertebral artery; BA, basilar artery; MCAo, middle cerebral artery occlusion; pMCAo, permanent middle cerebral artery occlusion; tMCAo, transient middle cerebral artery occlusion.

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1. Introduction

Stroke is one of the leading causes of death and long-term disability worldwide (Feigin et al., 2014). With its significant disease burden, the treatment of stroke has been extensively studied and it has undergone significant changes throughout the years. Recent exciting developments in the field with endovascular treatments have shown excellent outcomes in acute ischemic stroke; this includes the use of the novel stent retriever (Gounis et al., 2013; Saver et al., 2015). Prior to translating these treatments to human populations, a large-animal ischemic stroke model is needed to gather important information about the safety and efficacy of these endovascular procedures.

A variety of large-animal stroke models, such as non-human primates (NHP), canines, felines, ovis, swine, and leporidae, have been extensively used over the course of several decades to understand the disease process involved in stroke, and also to develop novel treatments that can translate to humans (Cook and Tymianski, 2012; Culp et al., 2013; Duberstein et al., 2014; Boltze et al., 2008; Hayakawa and Waltz, 1975). In choosing animal models that closely resemble humans, there are several factors that need to be considered, not only economically and anatomically, but also ethically. This is especially the case for NHP, where ethical components are the most common barrier to using this model, next to the high costs associated with this particular population (Coors et al., 2010). This is why canine models are preferred among many research groups when studying various facets of stroke.

Historically, canine stroke models were established by directly injecting cells into the carotid artery to occlude the vessels (Hill et al., 1955). With the advent of new technologies in digital subtraction angiography, less invasive endovascular stroke models have been developed. Multiple methods have been proposed to induce stroke in canine subjects, including angiography-guided embolus injection and coil embolization of the cerebral arteries (Shaibani et al., 2006; Rink et al., 2008).

In this review, we aim to evaluate all of the available literature associated with the endovascular technique of inducing stroke in a canine model.

2. Why canines?

One of the most common forms of acute ischemic stroke results from large artery occlusion. This disease state is difficult to mimic ex vivo, and the data on the safety and feasibility of intra-arterial techniques cannot be obtained from non-animal studies. To date, there have been large numbers of animal stroke model trials that showed promising results for future therapeutic techniques, but they failed to translate into successful treatments in humans (Kahle and Bix, 2012). Per the recommendations from the Stroke Therapy Academic Industry Roundtable (STAIR), testing in a large-animal species with anatomy that more closely resembles that of humans shows promise in addressing this failed translational gap (Stroke Therapy Academic Industry R., 1999).

Canines exhibit a number of characteristics that render them one of the ideal species for use after small-animal studies, but before beginning human clinical trials. Canines have a gyrencephalic brain with a proportion of gray/white matter that more closely resembles that of humans than the lissencephalic brains of small animals (Ferrer et al., 1986; Wynshaw-Boris et al., 2010). The anatomical disparity between rodent and human brains makes rodent stroke model research difficult to translate to humans.

The neurovascular anatomy of canines enables their arteries to be catheterized in a similar manner to humans under angiographic guidance, allowing for minimally invasive endovascular stroke induction and stem cell delivery surgeries (Rink et al., 2008). Endovascular procedure evaluation is very limited in small-animal models due to the small size of the cervical and cranial arteries in these animals; as such, the procedure cannot be visualized in real time by angiography. Other large-animal species such as felines, ovis, and swine have a well-developed carotid rete mirabile, a fine vascular network that supplies the cerebral arteries (Gillilan, 1976; Gralla et al., 2006). This is an obstacle when advancing endovascular catheters and devices to the cranial arteries, particularly in the middle cerebral artery (MCA), which is the target of most stroke models. In these species, it is necessary to perform invasive craniotomy to access the MCA (Wells, 2012). Structures such as the eye (which often is enucleated), temporalis muscle, and zygomatic arch suffer damage under this method (Howells et al., 2010). Other disadvantages include the fact that the skull needs to be opened, ultimately affecting cerebral pressures; moreover, the dura mater is breached and cerebrospinal fluid is lost.

NHP are an ideal model for ischemic stroke research due to their close relation to humans and the similarity of their brains. Table 1 summarized the differences in utilizing canine and NHP as stroke models. The disadvantages of using NHP models include the costly maintenance fees, and the use of NHPs also raises more ethical concerns than the use of canines (Coors et al., 2010; Tong et al., 2015; Quigley, 2007). Even so, medical experiments on canines still carry major ethical considerations in the current era, as canines are considered “man’s best friend”, and society expresses concerns about the usage of canines when compared to other animals, such as rodents (Hasiwa et al., 2011).

3. Canine cerebral artery supply

The canine brain is supplied by a cerebral arterial circle system, consisting of anterior and posterior circulation (Budras et al., 2002). The anterior circulation consists of the anterior/rostral cerebral arteries (ACA), anterior communicating artery, internal carotid arteries (ICA), and MCA. The ICA is approximately half the size of the external carotid artery (ECA). The ICA enters the skull through the posterior foramen lacerum, travels through the carotid canal, and continues to be surrounded by the cavernous sinus, where it is joined by the ramus anastomicus, a branch of the maxillary artery. Beyond this point, the ICA forms an S-shaped curve and joins the cerebral arterial circle. Approaching the MCA via the ICA is relatively difficult due to the tortuosity of the canine ICA (Rink et al., 2008). The canine MCA also receives more significant leptomeningeal circulation from the ipsilateral ACA and posterior/caudal cerebral artery (PCA), and significant maxilla–carotid collateral circulation is also present in canines when compared to humans, which is one difficulty that is faced when trying to repeat lesion sizes (Symon, 1960).

The posterior circulation is formed by the basilar artery (BA) caudally and the PCA (Budras et al., 2002). The BA is formed after the vertebral arteries (VA) fuse at the level of the first cervical nerve origin. The canine BA has a uniform diameter throughout and is straight enough to accommodate endovascular devices, which is why this route is used more commonly than the anterior circulation to reach the MCA. Superior/Rostral cerebellar arteries and inferior/caudal cerebellar arteries both branch from the BA with some variations. Fig. 1 shows the canine cerebral arterial supply.

The most common canine breeds used in canine endovascular stroke models are mongrels (weight range: 13–37 kg) or beagles (weight range: 9–15 kg). Many factors should be considered when choosing canine breed and size for an endovascular stroke model. Smaller canines have many disadvantages; for instance, it is more difficult to gain femoral access, and these animals also have a smaller caliber of intracranial vasculature. Conversely, larger canines can be more costly.