Longitudinally Characterization of Perfusion, Diffusion, and Cerebral Vascular Reactivity in Nonhuman Primate (Baboon) Stroke

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Introduction Numerous interventions have been shown to be effective in treating ischemic brain injury in rodent stroke models, but all failed to advance to clinical practice except rtPA. The rodent stroke models may not adequately reflect the complexity of human stroke (1). Non-human primates (NHPs) are likely to more faithfully recapture human stroke because NHPs are evolutionary close to humans and have very similar vascular anatomy to humans. There are a number of dissimilarities between the rodent and human brain that may lead to differences in response to identical ischemic insults. Timing, dose and other aspects of pharmacokinetics in humans could not be easily extrapolated from rodent models. The goal of this study was to describe the development of a large NHP (baboon) stroke model, to characterize the spatiotemporal progression of ischemic lesion using multimodal MRI on a clinical scanner. The baboon brain is 45% larger brain than rhesus brain. Specifically, we aimed to depict lesion growth, perfusion-diffusion mismatch, and cerebral vascular reactivity (CVR, an index for integrity of cerebrovascular autoregulation [2,3]) in permanent and transient stroke. Improved understanding of the lesion evolution and its characteristics longitudinally in clinically relevant model of stroke might provide important information to better guide clinical diagnosis, test novel interventions and improve treatment time windows.

Methods Seven normal female baboons (16-23 kg) were subjected to permanent (n=4) or transient (n=3) middle cerebral artery occlusion (MCAO) using an endovascular approach that involves minimal invasiveness. Briefly, the guide wires and microcatheters were advanced under the guidance of x-ray angiography and a balloon microcatheter was inflated after the position was confirmed. Reperfusion was achieved by deflating and withdrawing the balloon catheter after 60-min or 90-min of MCAO. Immediately after stroke induction, the animal was transported to the MRI for follow-up scans. Animals were anesthetized with ~2% isoflurane during stroke surgery and 0.8~1.0% isoflurane with vecuronium (0.1mg/kg) during MRI. MRI studies were performed on a clinical 3T Siemens TIM-Trio with a standard 12ch human head coil. Multimodal MRI including anatomical (T2 FLAIR and T1 MPRAGE), perfusion (pCASL), diffusion MRI, and MRA were acquired. Hypercapnia was introduced through a pre-mix 5% CO_2 tank with 2 min baseline and 4 min "stimulation" during perfusion scans. CVR is defined as percent signal differences before and after CO_2 inhalation. Images acquisition started from 1-hour post-reperfusion up to 6 hours (permanent MCAO) or 3 hours (transient MCAO). One set of images were obtained every 30 min. Follow-up MRI on day 1, 3, 7, and 30 were also acquired in the transient MCAO group. Data were processed using codes written in Matlab. CBF and ADC maps were calculated. Final infarct was determined on T2-FLAIR images on each of their last time point before euthanasia (6 hr or 24 hr for permanent MCAO and day 30 for transient MCAO). Lesion volumes (LV) were determined by three independent observers manually drawing region-of-interests (ROIs). ROIs of the infarct defined by the endpoint T2-FLAIR images were used for plotting temporal progression of MRI parameters.

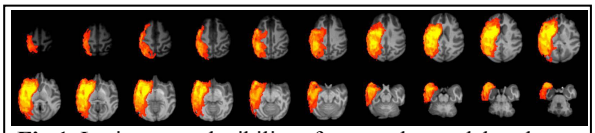

Fig 1. Lesion reproducibility of our stroke model under permanent stroke. (yellow means 100% overlap, n=4).

Results and Discussion This study describes a new clinical relevant NHP stroke model in baboon with minimum invasiveness, which is suitable for MRI studies. The lesion is highly reproducible with over 90% lesion overlap in permanent stroke (**Fig 1**). Multimodal MRI to longitudinally characterize ischemic evolution and the perfusion-diffusion mismatch was also optimized and implemented.

Quantitative perfusion and diffusion analysis shows that, in the normal hemisphere, CBF and ADC remained unchanged across all time points ($p>0.05$). In permanent MCAO (**Fig 2**), a perfusion-diffusion mismatch was observed. The mismatch was large, grew smaller over time, and disappeared by 6 hours post occlusion. This temporal profile is distinct from rodent stroke (~3 hr), but is similar to humans. The average final infract volume was ~29 mL (~17% of total brain volume). In transient MCAO, lesion volume defined by ADC decreased over time on day 0 and peaked at 24 hr post reperfusion followed by a secondary decrease on day 3 and 7 due to ADC renormalization. The average final infarct volume defined by T2 FLAIR was ~4 mL (~2.5% of total brain volume), indicating that reperfusion salvaged substantial mismatch compared to permanent MCAO.

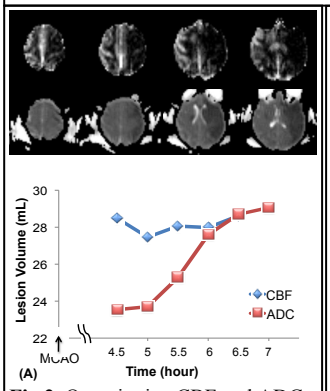

Fig 2. Quantitative CBF and ADC maps depict PWI-DWI mismatch and the lesion volume evolution from a permanent MCAO animal,

Fig 3 shows the longitudinal quantitative CBF and ADC maps from one representative animal underwent 60-min MCAO. In transient MCAO, both acute and chronic post-ischemic hyperperfusion (PIH) were observed. By comparing the CBF and ADC maps at the same time point (row), PIH was larger than the hypointense ADC territory in the hyper-acute phase, but it matched at later time points in the chronic phase (day 1 and 3). This suggested that *early* PIH was malignant and caused subsequent injury or appeared as a by-product of other cascade of irreversible injury. A reversible early peri-PIH hypoperfusion also present, which might due to temporary vascular events (e.g. vasospasm or loss of vascular autoregulation) or the "no-reflow" effects associated with ischemia. CVR within ischemic territory was lost in permanent stroke. However, in the peri-infarct regions in transient stroke, BOLD-CVR and CBF-CVR differed. Regions with positive CBF-CVR but negative BOLD-CVR were salvaged, as opposed to tissues with BOLD-CVR and CBF-CVR changes in the same direction and eventually infarcted.

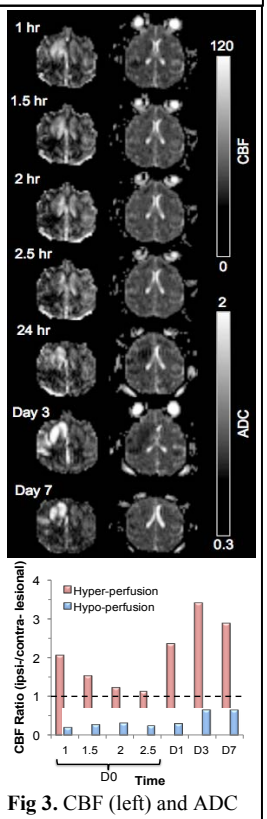

Fig 3. CBF (left) and ADC (right) maps from a subject, and the ipsilateral to contralateral ratios of hyper- and hypo-perfusion

Conclusion This study offers encouraging results to further explore multimodal MRI of NHP stroke model longitudinally. Future studies will increase sample size, establish ADC and CBF viability thresholds, include other multimodal MRI (i.e. fMRI), investigate different MCAO durations to mimic various clinical conditions and evaluate functional reorganization in chronic stroke.

References: [1] Fisher et al., Stroke, 1999. [2] Zhao et al., Neurology (2009). [3] Imaizumi et al., Annals Nucl Med (2004).