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Retro-engineering an intra-arterial pharmacotherapy administration mouse model to mimic the human condition of endovascular thrombectomy for treatment of acute ischemic stroke.

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Introduction

Stroke is the 5th leading cause of death in the U.S. with 130,000 deaths and 795,000 affected annually. At present there is a significant disconnect between basic stroke research and clinical stroke therapeutic needs. To bridge this divide, we have retro-engineered a mouse model of stroke from clinical ischemic stroke thrombectomy for selective intra-arterial pharmacotherapy administration.

Stroke & Intra-arterial Model

Methods

- Model developed to mimic the clinical condition of endovascular thrombectomy and intra-arterial pharmacotherapy administration through an experimental mouse model of stroke.
- Male C57/Bl6 mice 16 weeks old underwent a transient tandem ipsilateral CCA/MCA occlusion (MCAO) for 1 hour.
- Isolation of the ECA/ICA and micro-angio tubing insertion.
- Intra-arterial injection of Carbon Black Ink (1:9).
- Intra-arterial injection of Verapamil (0.15mg/kg), a calcium channel blocker at optimized flow rate and injection volume.

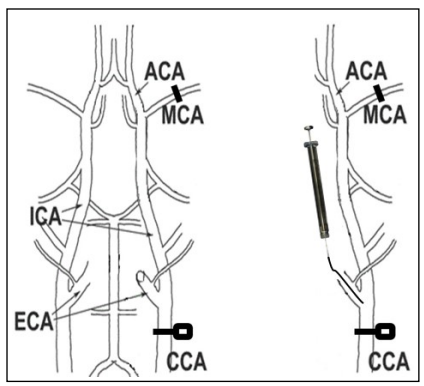


Figure 1. MCAO model (Steele et al.)

Figure 2. Intra-arterial model (Steele et al.)

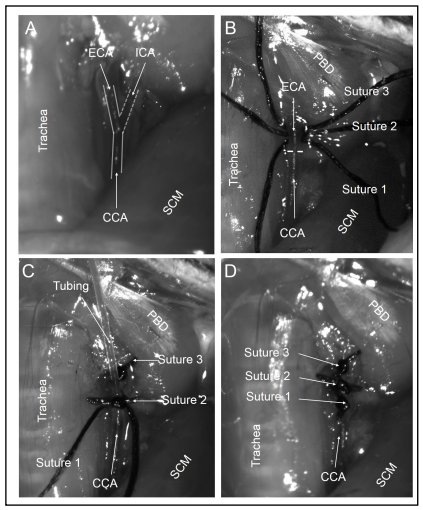


Figure 3. A. Outline of CCA branching into ICA and ECA., B. Placement of sutures under ECA., C. Insertion of tubing into ECA and securing of sutures., D. Completed surgery with suture ligation. (Maniskas et al.)

Laser Doppler & Speckle

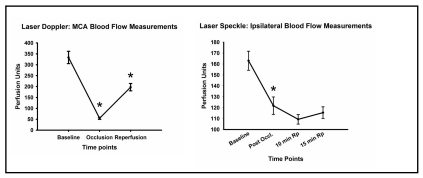


Figure 4. A. Laser Doppler MCA blood flow. B. Laser Speckle ipsilateral blood flow.

Results

Flow Rate & Injection Volume

Injection Rate (uL/min)	Injection Volume (uL)	MCA Staining?		Hemispheric Staining?		
		Ipsilateral	Contralateral	Ipsilateral	Contralateral	Liver Staining
10.0	100	Yes	Yes	Yes	Yes	Yes
7.5	100	Yes	Yes	Yes	Yes	Yes
5.0	100	Yes	Yes	Yes	Yes	Yes
2.5	100	Yes	Yes	Yes	Yes	Yes
1.0*	100	N/A	N/A	N/A	N/A	N/A
10.0	50	Yes	Yes	Yes	Yes	Yes
7.5	50	Yes	Yes	Yes	Yes	Yes
5.0	50	Yes	Yes	Yes	Yes	Yes
2.5	50	Yes	Yes	Yes	Yes	Yes
2.5	25	Yes	Slight	Yes	Slight	Slight
2.5	10	Yes	No	Yes	Slight*	No

Table 1. IA flow rate and injection volume.

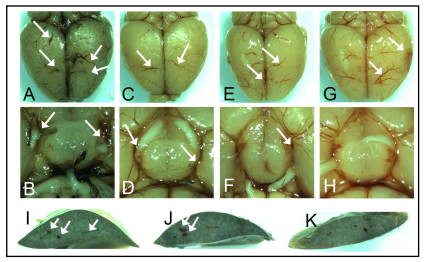


Figure 5. Dorsal and Circle of Willis View: A/B. Flow Rate (FR) 10.0 µL/min Injection Volume (IV) 100 µl, C/D. FR 5.0 µL/min IV 50 µl, E/F. 2.5 µL/min IV 25 µL, G/H. FR 10.0 µL/min IV 10 µL/min.

Cross Section of Liver: I. FR 10.0 µL/min IV 100 µl, J. 5.0 µL/min IV 50 µl, K. 10.0 µL/min IV 10 µL/min.

Infarct Volume

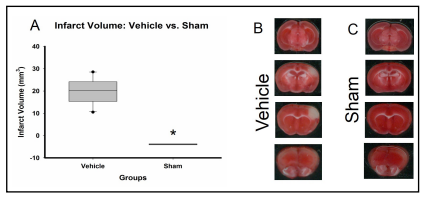


Figure 6. A. Infarct volume (mm3) measurements for MCAO mouse model with IA administration of saline at flow rate 2.5 µl/min and injection volume 10 µl (n of 15 for vehicle and n of 5 for sham). B/C. Representative images of TTC stained brains from vehicle and sham animals.

Neuroprotective Agent

Physiological Measurements

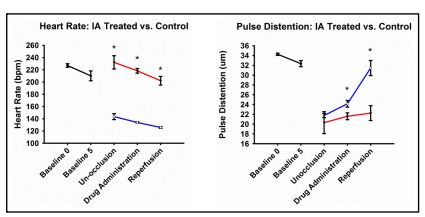
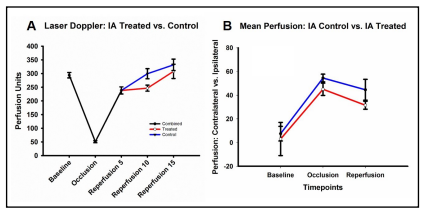


Figure 7. MouseOx Plus. A. Heart rate for treated versus control. B. Pulse distention for treated versus control.

Laser Doppler & Speckle



Behavioral Outcome

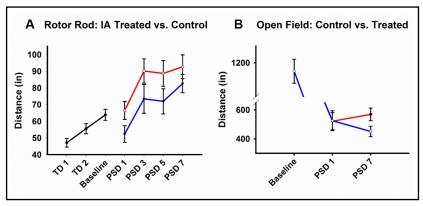


Figure 8. Laser Doppler & Speckle. A. Laser Doppler blood flow measurement of MCA pre and post occlusion in treated versus control., B. Laser Speckle hemispheric blood flow measurements contralateral versus ipsilateral in treated versus control.

Figure 9. Behavior A. Rotor Rod forced movement test for treated versus control., B. Open Field free roam test for treated versus control.

Infarct Volume

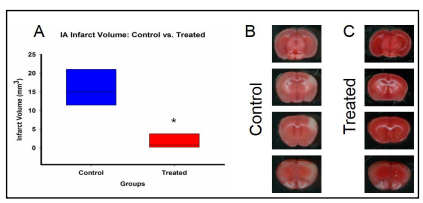


Figure 10. Infarct Analysis. A.Infarct volume (mm3) for treated versus control., B. TTC image of control brain., C. TTC image of treated brain.

*** indicates a P value of P<0.05**

Learning Objectives

1) Understand the need for a valid bedside-to-bench translational model for stroke and thrombectomy.
2) Learn the steps involved to recreate stroke - recanalization - selective intra-arterial drug administration.
3) Evaluate the methods for validation of the stroke model.
4) Learn about the application of a stroke model in studying a known drug for neuroprotection.
5) Understand how the model facilitates translation to a clinical study.

Conclusions

We demonstrate for the first time, the combination of a tandem common carotid-middle cerebral artery model of acute ischemic stroke with selective ipsilateral intra-arterial drug administration. This model mirrors the clinical condition of Stroke -> Acute Thrombectomy -> Selective Immediate IA Drug Administration. It provides an opportunity for pre-clinical evaluation of drug therapy to augment current standard of care (thrombectomy). We also show its applicability as a model to bridge the translational gap from laboratory study of a neuroprotective drug class (calcium-channel blockers) to the clinical scenario (SAVER I study).

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