Real Time Physiologic Monitoring of Intra Arterial rtPA Therapy in a Canine Model of Acute Embolic Stroke

M. Rohany[1], A. Shaibani[1], W. Shin[1], T. Cashen[1], K. R. Harris[1], T. J. Carroll[1]
[1]Northwestern University, Chicago, IL, United States

Introduction:

Stroke is one of the most important challenges of medical field since it is the third death cause in United States. Intrarterial recombinant tissue plasminogen activator (IA rtPA) is the only FDA approved therapy for acute ischemic stroke that improve the outcome (1). Multiple studies of acute stroke have shown that in addition to a "core" of irreversibly infracted tissue, there are surrounding areas, which are ischemic but still viable. Studies have also demonstrated that areas of benign oligemia may also be present, which would not progress to infarction (2). Achieving treatment strategies allowing simultaneous monitoring of treatment effectiveness requires imaging techniques capable of differentiating the infarct core, the ischemic penumbra and areas of benign oligemia. The increasingly important role of Magnetic Resonance (MR) perfusion and diffusion imaging in understanding the pathophysiology of stroke (3) caused increasing attention to combined MR-IR suites as a future management standard in acute stroke. In this study we demonstrate a MR compatible canine model for real time physiologic monitoring of IA rtPA thrombolytic therapy by measuring Apparent Diffusion Coefficient (ADC) values and quantitative cerebral blood flow (qCBF) values in infarcted regions during the IA rtPA injection.

Methods:

Total four dogs were involved in the study. Autologos thrombus was prepared mixing each dog's blood sample with thrombin. The blood clots were directed to internal carotid artery thorough an intraarterial catheter to simulate an acute embolic infarction. Digital Subtraction Angiography (DSA) documented the arterial vessel occlusion. IA rtPA injection started 3 hours after introducing the blood clots as a 2 mg bolus injection of rtPA (Activase, Genentech, San Francisco, CA, USA),followed by a 6 mg infusion performed over 45 min Serial MRI imaging was performed to track possible changes the ADC and qCBF values after IA rtPA injection.
Serial DWI/PWI images were acquired at 30-minute intervals to track the evolution of diffusion changes in the region affected by the stroke, and to detect any perfusion changes in response to treatment. Due to anatomic differences between humans and dogs, the DWI/PWI images were acquired in the coronal plane. The parameters for the DWI images were: TR/TE = 3000 ms/97 ms, BW = 1220 Hz/pixel, Field of View (FOV) = 148 cm x 148 cm, b-values = 0 sec/mm2, 500 sec/mm2, 1000sec/mm2, matrix = 128 x 128, 15, 5 mm thick slices were acquired with no skip between slices.
The PWI images were co-localized to the central slices of the diffusion images using the scanners scan prescription tools. The PWI scans were adapted from the clinical protocol used at our site (2D, Gradient Echo EPI, TR/TE= 1150 ms/52 ms, bandwidth = 1260 Hz/pixel, 9-10, 5 mm slices, 50 phases acquired). For perfusion images, 0.1 mmol/kg body weight of a gadolinium based contrast agent (Magnevist, Berlex, Princeton, NJ) were injected at 2.0 ml/sec through the catheter placed in the left ventricle. Upon completion of the IA rtPA infusion, a final DWI/PWI image set was acquired.

Results:

Brain tissue infarction confirmed by DSA in all four dogs
Recanalization as defined by the restoration of blood flow to
in all four dogs after IA rtPA injection. The regions of
relCBF correlate with the abnormalities observed in the DWI
We found the mean value of ADC in the hypoperfused
sec/mm^2, mean $^+/_-$ STD) to be significantly different ($p<0.05$)
values (ADC = 80.40 +/- 8.56 sec/mm^2, mean $^+/_-$ STD). The
stroke and contralateral normal ROIs was 42.25 $^+/_-$ 8.64
and 7.22 $^+/_-$4.90 ml/min/100g (mean $^+/_-$ STD) respectively.
to be statistically significant ($p< 0.0007$). Figure 1 shows
images in one of our experiments were recanalization was
acquired at two hours, confirms a region of reduced ADC
the blood clots (1a). After completion of IA rtPA injection,
in the affected territory the infarcted region observed by
Post processed images of qCBF calculations before and after
perfusion improvement in the stroke region to a value which
for ischemic stroke (Figs 1(c) and 1(d) respectively).

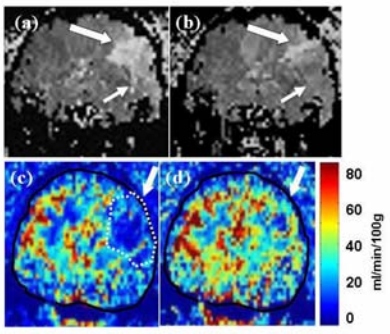

Fig 1: The ADC image acquired at two hours, confirms a region of reduced ADC due to infarct after introducing the blood clots (a). After completion of IA rtPA injection, marked improvement of flow in the affected territory the infarcted region observed by increased ADC values (b). Post processed images of qCBF calculations before and after IA rtPA injection showed perfusion improvement in the stroke region to a value which is above the known threshold for ischemic stroke. (c,d).

after delivering blood clots.
the affected area was observed
prolonged TTP and reduced
images (b=1000 and ADC).
region (ADC = 53.49 $^+/_-$ 12.52
than the normal contralateral
mean values of qCBF in the
ml/min/100g (mean $^+/_-$ STD)
These differences were found
the pre-and post treatment
observed. The ADC image
due to infarct after introducing
marked improvement of flow
increased ADC values (1b).
IA rtPA injection showed
is above the known threshold

Discussion/Conclusions:

We have developed a reproducible MRI compatible canine model of embolic stroke for real time physiologic monitoring of IA rtPA thrombolytic therapy. We showed effectiveness of the IA rtPA injection therapy in restoration of the blood flow in the infarcted region. We also demonstrated the feasibility of the IA rtPA injection therapy monitoring using qCBF and ADC values measurements by MR imaging techniques. These finding might help to develop more effective thrombolytic treatment monitoring in stroke patients.

References:

1. Noser EA, Shaltoni HM, Hall CE, et al. Aggressive Mechanical Clot Disruption: A Safe Adjunct to Thrombolytic Therapy in Acute Stroke? Stroke 2005; 36:292-296.
2. Sobesky J, Weber OZ, Lehnhardt F-G, et al. Does the Mismatch Match the Penumbra?: Magnetic Resonance Imaging and Positron Emission Tomography in Early Ischemic Stroke. Stroke 2005; 36:980-985.
3. Schellinger PD, Jansen O, Fiebach JB, et al. Feasibility and Practicality of MR Imaging of Stroke in the Management of Hyperacute Cerebral Ischemia. AJNR Am J Neuroradiol 2000; 21:1184-1189.