Diffusion-Perfusion MRI and X-ray Angiography of rt-PA Treatment in Rats : Dependence of Stroke Volume on Recanalisation

Christian Beaulieu[1,2], Elmar Busch[1,3], Alex de Crespigny[1], Frank Wiegand[3], Michael Moseley[1]
[1]Dept. of Radiology, Stanford University, USA; [2]Dept. of Biomedical Engineering, University of Alberta, Canada;
[3]Neurologische Universitaetsklinik, Essen, Germany

Introduction

The role of recombinant tissue plasminogen activator (rt-PA) in thrombolytic treatment of acute ischemic stroke is poorly understood. Diffusion and perfusion MRI studies of experimental embolic stroke models have demonstrated improved reperfusion after thrombolytic treatment albeit with variable degrees of recovery of lesion volume (1-5). The improvement in lesion volume or lack thereof has not been directly related to the success or failure of the thrombolytic agent in recanalising (i.e. reopening) the occluded blood vessel. The purpose of this report is to evaluate the relationship between rt-PA treatment, blood vessel patency (assessed by X-ray angiography), perfusion, and lesion volume (on diffusion imaging) in an embolic stroke model in rats.

Methods

Sprague-Dawley rats (n=15, 330-380 g) were intubated, anaesthetised with halothane, and underwent thromboembolic stroke by injection of autologous blood clots (6). X-ray angiography was performed immediately after embolisation to confirm occlusion of the middle cerebral artery (MCA). Rats were transferred to the MRI suite and MR images were acquired within 1 h (before rt-PA) and every hour up to 6 h. X-ray angiography was repeated after the final MRI scan to determine patency of the ipsilateral MCA. The brains were then perfusion-fixed and processed for histology. Treatment with rt-PA (15 mg/kg b.w.) (n=8) or saline (n=7) commenced at 1 h post-embolisation and the infusion was given over 90 min.

Isotropic diffusion-weighted spin-echo imaging (DWI) {128x128, FOV = 50mm, TR = 2.5s, TE = 80ms, eight 1.5mm slices, b=1300s/mm^2} and perfusion-weighted imaging (PWI) {bolus tracking, gradient-echo EPI, 64x64, FOV = 40mm, TR = 1s, TE = 40ms, three 1.7mm slices) were performed on a 2 T Bruker Omega CSI spectrometer.

The ischemic lesion volume was measured as regions with a reduction of the apparent diffusion coefficient below 80% of the normal contralateral side. The bolus peak ratio (BPR = max signal loss ischemic side / max signal loss normal side) of the bolus tracking curves was used as an assessment of the degree of perfusion abnormality on a central slice. Patency of the ipsi-lateral MCA was assessed visually on the x-ray subtraction angiograms.

Results and Discussion

Based on the x-ray angiography observations at 6 h, the rats were separated into four groups: a) control with spontaneous recanalisation (n=2), b) rt-PA with recanalisation (n=3), c) control without recanalisation (n=5), and d) rt-PA without recanalisation (n=5). Groups a) and b) with recanalisation had improved perfusion values and smaller lesion volumes than the control group c). Groups c) and d) without recanalisation had poor perfusion values throughout the 6 h. However, rt-PA treatment without recanalisation resulted in *larger* final infarct volume than saline treatment without recanalisation despite similar lesion volumes on DWI at 30 min (Fig 1). This is consistent with reports of potential harmful effects (e.g. neurotoxic) of rt-PA (7).

In conclusion, the combination of diffusion and perfusion MRI with x-ray angiography has provided new insight into the effects of thrombolytic stroke therapy. As might be expected, perfusion is clearly improved and lesion volumes are smaller when rt-PA induces successful recanalisation. However, when recanalisation is not successful, rt-PA appears to be detrimental.

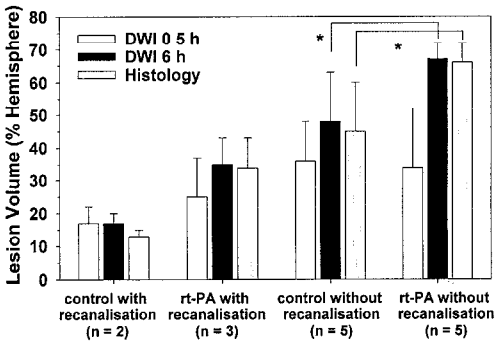

Figure 1: Lesion volumes at 6 h are larger in rt-PA treated rats without recanalisation of the middle cerebral artery (MCA) as compared to the control group without recanalisation (p=0.04 DWI 6h, p=0.03 histology). Rats with spontaneous or rt-PA induced recanalisation of the MCA demonstrate smaller lesion volumes.

References: 1 Yenari et al, JCBFM 17, 401 (1997), 2 Yenari et al, J Stroke Cerebr Dis 7, 179 (1998), 3 Busch et al, JCBFM 18, 407 (1998), 4 Takano et al, Neurology 50, 870 (1998), 5 Jiang et al, JCBFM 18, 758 (1998), 6 Busch et al, Brain Res 778, 16 (1997) 7 Wang et al, Nature Med 4, 28 (1998)

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