A MULTIPARAMETRIC MRI STUDY OF PARTIAL REPERFUSION FOLLOWING FOCAL CEREBRAL ISCHAEMIA IN THE RAT

D. A. West[1,2], E. Proctor[1], M. F. Lythgoe[1], R. J. Ordidge[2], D. G. Gadian[1]

[1]RCS Unit of Biophysics, University College London, London, United Kingdom, [2]Medical Physics and Bioengineering, University College London, London, United Kingdom

Introduction Reperfusion when induced in animal models of middle cerebral artery occlusion (MCAO) commonly differs quite markedly from that in human stroke. Upon the removal of the occluding device or suture, the restoration of blood flow takes place abruptly rather than as a gradual 're-circulation'. In humans with spontaneous or thrombolytic-induced reperfusion following stroke, recanalisation rates of 1-3 days are common[(1)]. There have been calls for increased clinical applicability of animal models of cerebral ischaemia in order to improve the likelihood of successful outcomes in clinical trails of novel stroke treatments[(2)]. We have used a recently developed rat MCAO model which produces ischaemia in the ipsilateral cortex only[(3,4)], to study 2 types of reperfusion; full and partial, with multiparametric MRI in acute experiments.

Materials & Methods 13 Male Sprague-Dawley rats (290-320g) were studied. General anaesthesia was induced with a mixture of 3% halothane in a 40:60 O_2/N_2O gas mixture and maintained using 0.75 to 1.25 % halothane. Remote controlled MCA and bilateral common carotid artery (CCA) occlusion was applied using a novel remote controlled technique[(3)]. Following 90 minutes of ischaemia one group of animals (n=7) was subjected to simultaneous de-occlusion of all three vessels (full-reperfusion group) and a second group (n=6) was subjected to reperfusion of the CCAs only (partial-reperfusion group), by remote-control for 135 minutes. Tissue water ADC, T_1, T_2, M_0 and CBF were serially measured and quantified throughout the baseline, occlusion and reperfusion periods. The rats were physiologically stable and spontaneously breathing throughout. Monitoring was via subcutaneous electrodes for heart and respiratory rate and temperature was monitored using a rectal thermocouple. Warm air heating was used to maintain the temperature at 37±0.5ºC. MR data were acquired using a 2.35T horizontal bore magnet interfaced to a SMIS console. ADC maps were calculated from trace-weighted single shot spin-echo EPI images with b=38 and b=872 s/mm^2. A continuous arterial spin labelling (CASL) technique was used to monitor CBF non-invasively[(5)] whereby flowing blood water spins were inverted in the neck using flow-driven adiabatic fast passage inversion[(6)]. T_1 was measured using a single shot IR-EPI sequence with TI=20, 100, 300, 500, 1000, 1800 and 2500ms, TR=6s, TE=18ms. The MASAGE-IEPI technique was used to measure T_2[(7)]. The imaging slice was 0.5mm caudal to bregma and was 1.6mm thick in all MRI acquisitions. Regions of interest were analysed in left (ipsilateral) and right (contralateral) MCA-supplied cortex, anterior cerebral artery (ACA) supplied cortex and sub-cortical grey matter. Animals were classified as completely or incompletely resolving dependent upon the ADC returning to >95% normal (pre-occlusion) levels in the ischaemic cortex following reperfusion.

Results CBF and T_2 time-courses for resolving ischaemic cortex differed significantly between the reperfusion groups (Figures 1 and 2). ADC, M_0 and T_1 changes were equivalent in both reperfusion groups. 2/7 (29%) of animals in the full-reperfusion group and 3/6 (50%) animals in the partial-reperfusion group showed patches of incomplete ADC resolution in the reperfusion period. These areas also showed persistent increases in T_2 and reductions in CBF throughout the reperfusion phase, compared to completely resolving areas. ADC, T_2 and CBF parameter images (maps) are shown below for a completely and incompletely resolving animal (Figure 3).

Figure 1. Ischaemic lesion CBF time-courses for full and partial reperfusion

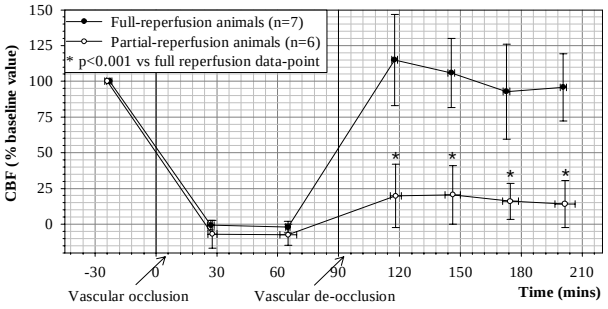


Figure 2. Ischaemic lesion T_2 time-courses for full and partial reperfusion

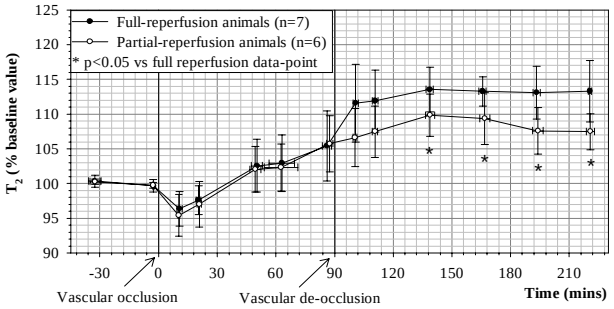
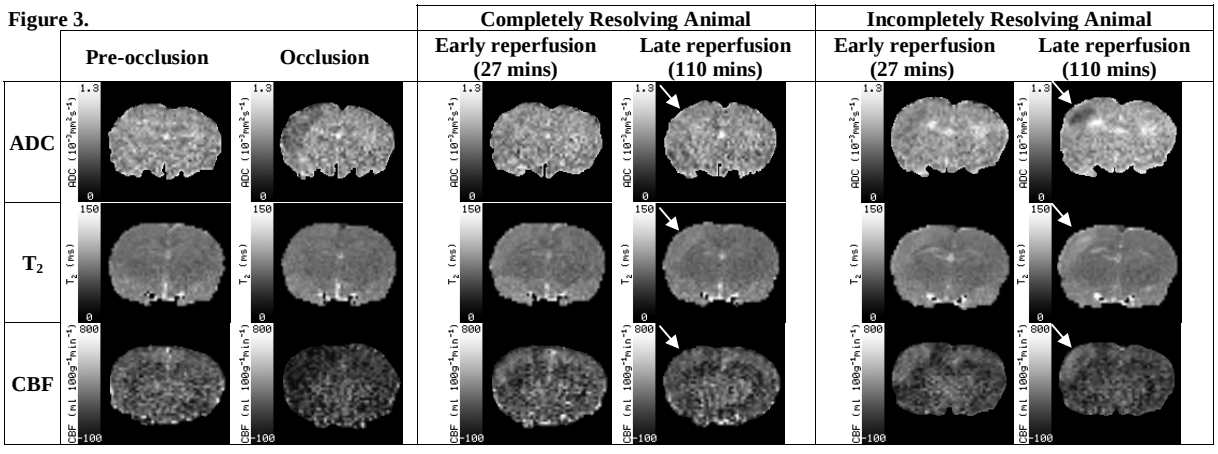


Figure 3.



Discussion The data show that limited reperfusion of ischaemic tissue can be induced by de-occluding the CCAs whilst maintaining MCAO in this animal model of stroke. Potential explanations for the observed T_2 differences between the two groups in the period following reperfusion include 'luxury perfusion' with increased CBV and oxygen saturation in the full-reperfusion group, or reduced vasogenic oedema formation in the partial reperfusion group due to lower perfusion pressure. The phenomenon of incomplete reversal of ADC changes in the reperfusion period which may be analogous to the no-reflow phenomenon[(8,9)] was seen in both reperfusion groups. These areas showed reduced perfusion, persistent increases in T_2 and reductions in ADC suggestive of ongoing ischaemia and oedema formation. These similarities to human ischaemic stroke may provide a useful basis for the further study of stroke pathogenesis and amelioration in the future.

References **1)** Rother J, Schellinger PD et al. Stroke 2002; 33: 2438-2445 **2)** Small DL, Buchan AM. Br.Med.Bull. 2000; 56: 307-317 **3)** West DA, Proctor E et al. Proc.ISMRM 10th Annual Meeting, Hawai'i 2002; 1241 **4)** West DA, Valentim LM et al. Proc.ISMRM 11th Annual Meeting, Toronto 2003; 1940 **5)** Thomas DL, Lythgoe MF et al. Phys.Med.Biol. 2000; 45: 97-138. **6)** Dixon WT, Du LN et al. Magn Reson.Med. 1986; 3: 454-462 **7)** Thomas DL, Lythgoe MF et al. Neuroimage. 2002; 15: 992-1002 **8)** Cerisoli M, Ruggeri F et al. J.Neurosurg.Sci. 1981; 25: 7-12 **9)** Hossmann KA. Shock 1997; 8: 95-101