The vascular and haemodynamic response following chronic hypoperfusion in the developing and mature rat

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Introduction Arterial occlusion is one of the main mechanisms leading to hypoperfusion. The severity of the hypoperfusion determines whether tissue will be oligaemic or ischaemic[1]. Vascular growth and the collateral circulation can compensate for arterial occlusion and possibly reduce the effects of hypoperfusion[2]. Vascular growth is an active process consisting of three distinct mechanisms: vasculogenesis, arteriogenesis and angiogenesis, and the balance between these processes during development has yet to be characterized. Aberrations in blood flow due to arterial occlusion have been identified in childhood pathologies (e.g. moyamoya syndrome)[3], yet there have been limited experimental investigations into the vascular response of the developing brain to arterial occlusion. For this study, we have investigated the chronic vascular and morphological changes due to arterial occlusion in both the mature and developing brain following bilateral common carotid occlusion (BCCAO) with MRI and histology.

Methods Four adult Sprague-Dawley (SD) rats were studied in experiments where CBF was measured before and immediately after BCCAO surgery. For chronic experiments 16 adult (3-months old) SD rats and 16 newborn pups (3-day old) SD rats were randomly divided into equal groups for BCCAO or sham control surgery. Animals were anaesthetised with 2.5% halothane and maintained on 1.75% halothane with 70/30% N_2O/O_2. Coronal images were obtained approximately 3.3mm from bregma on a 2.35T horizontal bore SMIS system. CASL[4]: 128 x 64pixels, 2mm slice thickness, 44 averages and T_1 fits using 8 different TI times with 22 averages. T_2: MASAGE-IEPI[5], 128 x 64pixels, 2mm slice thickness, 16 averages. Trace-weighted DWI: 128 x 64 pixels, 2mm slice thickness, 48 averages. High resolution spin-echo: 128 x 128pixels, 1mm slice thickness, 17 slices, FOV 30 x 30mm, 10 averages. TOF-MR angiography (MRA): 128 x 128 x 128pixels, FOV 25 x 25 x 30mm, visualisation by maximal intensity projection (MIP) software. Cerebrovasculature: Papaverine hydrochloride was injected intravenously to induce maximal dilatation and India ink was subsequently injected into the ascending aorta. The brains were removed and suspended in paraformaldehyde for inspection.

Results & Discussion There were significant reductions in CBF after BCCAO surgery in the cortices and hippocampi (~50%) and a 20% decrease in the thalami, but no reduction in the apparent diffusion coefficient (ADC) was observed; therefore oligaemic hypoperfusion was established. However, 6 months following surgery CBF was restored in both adult and pups (sham controls: 116 ± 27ml/100g/min, 78-160 ml/100g/min; operated: 124 ± 30 ml/100g/min, 74-176 ml/100g/min *(mean ± sd, range)*). Compared with sham-operated controls, no differences were observed in the ADC, T_1 or T_2 values 6 months post-surgery. These results were perhaps surprising as previous studies have suggested pathological change[6,7]. To investigate the underlying mechanism for the restoration of CBF to control values, we performed MRAs of the neck. As expected, signal from the common carotid arteries was present in the sham-operated rats, but was absent in the BCCAO animals (fig1b). Interestingly, signal from the vertebral arteries appeared to be enhanced and the presence of collateral formation was evident (fig.1b&d). Two observers blinded to the groupings of the animals evaluated the MRA images and reported more tortuous vertebral arteries in the BCCAO adults and more midline collaterals in the BCCAO pups ,indicating different extracerebral modes of adaptation dependent on the age at onset of the insult (fig.1d). Figure 2 shows the intracerebral vessel diameters of various arteries which make up the circle of Willis measured 6 months after surgery. Highly significant ($p<0.001$) differences were seen between sham-operated and BCCAO animals in the basilar, posterior cerebral, posterior communicating arteries and in the internal carotid and anterior cerebral arteries ($p<0.01$). Interestingly, no significant differences in vessel diameter were observed between adult and neonatal age-groups for any of the vessels measured (2-way ANOVA). However, visually the basilar artery in the neonatal group was less tortuous when compared to the adult. Our studies suggest that the developing and mature animal exhibit different patterns of arteriogenesis and that the BCCAO hypoperfusion model will be useful for investigating vascular events in response to vaso-occlusive disease. Furthermore, non-invasive MRI measurements of cerebral haemodynamics may provide a useful indicator of the homeostatic responses to chronic hypoperfusion.

fig.1

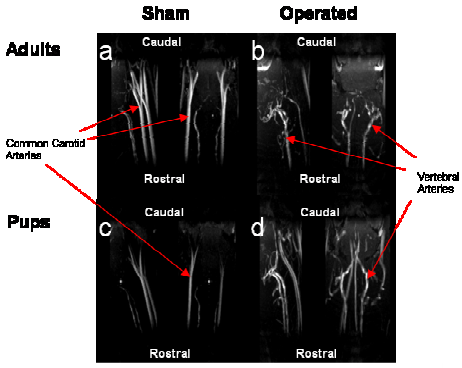

Figure 1 MRA MIPs of the neck 6 months following surgery. Sagittal plane (left in each frame) and axial (right). (a) Adult sham (b) Adult BCCAO (c) Pup sham (d) Pup BCCAO

fig.2

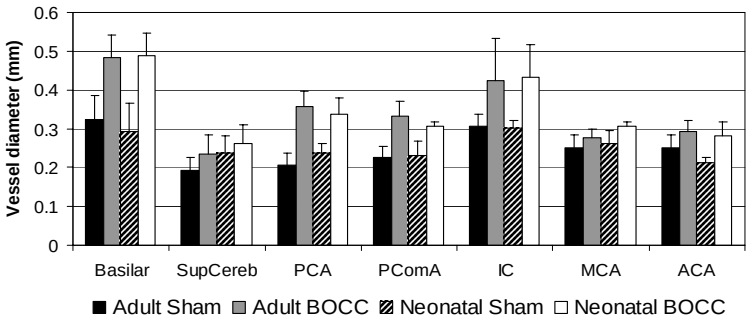

Figure 2: Diameter of the vessels comprising the Circle of Willis visualised by infusion of India ink. SupCereb = superior cerebellar artery, PCA = posterior cerebral artery, PComA = posterior communicating artery, IC = internal carotid artery, MCA = middle cerebral artery, ACA = anterior cerebral artery.

References [1]Lythgoe et al (2000) Magn Reson Med 44(5):706-712. [2]Busch et al (2003) J Cereb Blood Flow Metab. 23:621-628. [3]Calamante et al, A (2001) Stroke. 2810-2816. [4]Thomas et al (2000) *Phys Med Biol 45,8:R97-138* [5]Thomas *et al* (2002) *Neuroimage 15(4):992-1002.* [6]De la Torre et al (1993) Brain Research 623:6-15. [7]De Jong et al (1999) Neuroscience. 91:203-210.