Dynamic Oxygen-Enhanced T1-weighted MR in Tumour Xenografts

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BACKGROUND: Oxygen-enhanced (OE) MRI has potential as a biomarker of oxygen tension, hypoxia, or radiation resistance in human tumours but the mechanisms of contrast have not yet been fully elucidated.

PURPOSE To evaluate evidence for signal change from T_1 shortening due to dissolved molecular oxygen obtained from dynamic OE-MRI in tumour xenografts.

METHODS: ANIMAL PROTOCOL: In compliance with licenses issued under the UK Animals (Scientific Procedures) Act, male nude mice (N=5) with human glioblastoma xenografts (U87-MG) implanted on their right flank were anaesthetised with 1.6 – 1.9% isofluorane in either medical air, or 100% oxygen, throughout imaging. Temperature and respiration rate were maintenance used SA Instruments equipment.

MR PROTOCOL: Data were obtained using a 9.4T magnet (Varian Inova, USA) and 38 mm I.D. quadrature volume coil. T_1-weighted Signal Intensity (SI) was measured during air breathing and T_1 prior to the dynamic series was measured using a slice selective IR FLASH_sequence[1]: TR/TE= 21 ms/2.2 ms; flip angle = 20°; 2 averages, acq. matrix 128 x 64; inversion slice thickness = 20 mm; FOV = 30 mm x 30 mm; 4 sagittal slices, slice thickness 2 mm; inversion times (TI) of 0.01, 0.25, 0.5, 0.75, 1, 2, 5, 7, 9, and 12 s. Dynamic data were acquired using a T_1-weighted 2D FLASH sequence with the same parameters as the IR FLASH sequence, but with no inversion preparation. 192 volumes were acquired with a temporal resolution of 3s. 2 minutes into the dynamic acquisition, the anaesthetic carrier gas was switched from medical air to 100% oxygen for 6 minutes, then back to air for the remainder of the acquisition.

ANALYSIS: A whole tumour region of interest was selected on 4 slices of each tumour (n=5 mice). Signal intensity was calibrated for baseline T_1 and change in SI was recorded,. A two-tailed t-test of the mean values in each sample was performed to choose significantly increasing/decreasing voxels ($p<0.1$). All other voxels were classed as having no change. This approach gave acceptable parcellation of voxels: 8389 in the SI-increasing group, 15078 in the SI-decreasing group and 24832 in the no change group.

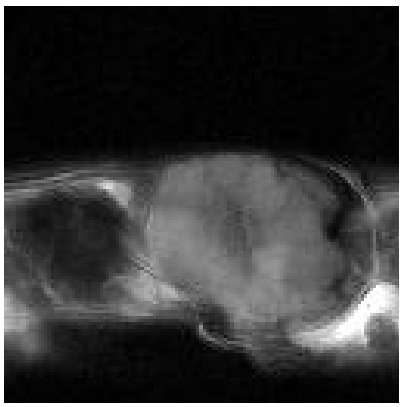

Fig.1. An example of a sagittal FSE image of a Flank-Mounted Tumour

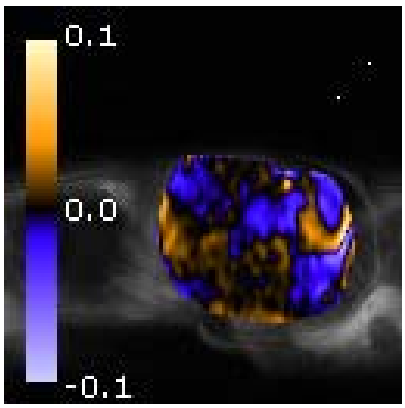

Fig. 2. An example of T_1-weighted SI changes (arbitrary units) in tumour xenograft of mouse breathing 100% oxygen compared to medical air. Blue - SI decrease; orange – SI increase

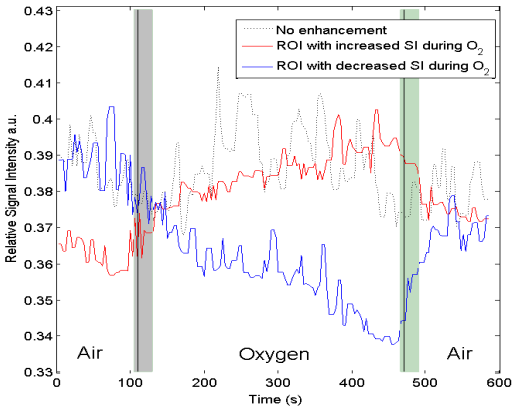

Fig.3. Dynamic oxygen-enhanced curves for the parcellation of T_1-weighted SI increase (red line), SI decrease (blue line) and no change (dotted line) under oxygen inhalation.

RESULTS: The U87 tumours had a multi-lobed structure, evident in pathological inspection and in FSE (Fig. 1) as well as in the SI change maps (Fig. 2). Figure 3 shows the average SI change over the 10-minute dynamic acquisition. The two parcelations showed opposite behaviour under 100% oxygen inhalation: SI increase or decrease. For the SI-increasing parcellation, T_1 before oxygen inhalation was higher than for the SI-decreasing parcellation.

DISCUSSION: All mice had large domains that exhibited the expected immediate increase in SI following the switch to oxygen inhalation, consistent with the expected T_1 decrease previously reported in human tumours[2]. These appeared to correspond to rims of the lobes and tended to have higher T_1 at baseline. However, there were also large domains, apparently at the centre of the lobes, where SI tended to decrease following the switch to oxygen inhalation. Indeed these domains dominated, so that the average SI change over all tumour voxels in all mice was negative. The interpretation of the SI-decreasing domains is unclear. They tended to have lower T_1 at baseline and may represent regions that are hypoxic at baseline: following the switch to oxygen inhalation, oxygenation of haemoglobin would increase while the concentration of dissolved oxygen remained negligible, compatible with results from the previously-described longitudinal relaxivity of paramagnetic deoxyhaemoglobin.[3] However, other explanations are possible, including vascular steal, fluctuating perfusion, or effects on SI from changes in T_2 or T_2*.

CONCLUSIONS: This study shows that dynamic T_1-weighted dynamic OE-MRI has potential to be used for monitoring regional changes of oxygen delivery and accumulation switching from medical air to 100% oxygen in experimental tumour, non-invasively.

REFERENCES: 1: Haase *et al*, *Magn Reson Med,* **13**: 77-89, 1990. 2: O'Connor *et al.* ISMRM 1441, 2008. 3: Meyer *et al*, *Magn Reson Med.*, **34**: 234-41, 1995.