Modulation of tumour R_1: a novel biomarker of oxygenation status

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Introduction There is considerable current interest in developing imaging biomarkers of tumour perfusion and oxygenation status[1]. Here we describe oxygen-induced modulation of tumour longitudinal relaxation rate (R_1) – an effect previously described in normal tissues[2, 3] – that is distinct from the blood oxygenation level dependent (BOLD) technique. We present initial results from a cohort of patients with advanced solid tumours.

Methods Ethical approval was obtained. Patients were imaged on a Philips Intera system (Philips Medical Systems, Best, Netherlands) at 1.5 Tesla. Five patients with advanced solid tumours were recruited (all female; mean age 62.6 years). Only lesions that were ≥ 3cm in-plane and present on at least 3 consecutive slices were included. Initial T_1-weighted and T_2-weighted anatomical sequences were performed to delineate the tumours.

Subjects breathed medical air (21% oxygen) for 8 minutes followed by 16 minutes breathing 100% oxygen and then a second phase of medical air for 8 minutes. Both gases were delivered at 15 l/min through a non re-breathing circuit with reservoir mask. During this period, the whole body transmit/receive coil was selected for transmission and reception. Series of 3D T_1-weighted fast field echo images were acquired (*TR* 3.5 ms, *TE* 0.9 ms, α= 2°/ 8°/ 17°, one average, FOV of 375mm x 375mm, matrix 128 x 128, 4 mm slice thickness, 25 slices) to estimate tissue T_1. Twenty four baseline measurements were collected while breathing medical air, followed by 48 on 100% oxygen, and then a further 24 back on medical air. Total acquisition time for each T_1 measurement was 19.5 s. Measurements were acquired during gentle breathing without breath holding. Finally, 0.1mmol/kg of Omniscan (Amersham Health, Amersham, UK) was administered intravenously through a power injector at 3 ml/s. Dynamic contrast-enhanced MRI (DCE-MRI) was performed (*TR* 4.0 ms, *TE* 0.82 ms, α= 20°, same average, FOV, matrix and slice thickness as for gas inhalation protocol) following fast field echo calculation baseline of T_1 with flip angles 2°/10°/20°/30° and 4 NSA. DCE-MRI temporal resolution was 4.97 s.

Image analysis was performed using a voxel-by-voxel fitting process with in-house software[3]. T_1 maps at each time point were generated using the variable flip angle method[4]. Tumour volumes were identified from the T_1-weighted and the T_2-weighted anatomical images and a volume of interest (VOI) was drawn to encompass the entire lesion. Change in the longitudinal relaxation rate ($\Delta R_1(t) = R_1(t) - R_1(air)$) was calculated for each time-point, as described previously[3]. ΔR_1 is proportional to the change in oxygen concentration at time point *(t)*, with the constant of proportionality being r_1 – the longitudinal relaxivity constant for oxygen. $R_1(t)$ is the R_1 value at each time point and $R_1(air)$ is the mean baseline R_1 value while breathing air. Mean ΔR_1 between baseline values and while breathing oxygen was calculated for each tumour and across the group. Significance of measured change in R_1 for each tumour time series was tested by a one-way analysis of variance in *SPSS 13.0*. IAUC and K^{trans} were calculated using the extended Tofts model with an assumed arterial input function[5] and were assessed for correlation with oxygen-induced ΔR_1 using *Spearman's rho*.

Results The imaging protocol was well tolerated by all subjects. In total, seven lesions were identified (see Table 1). Mean ΔR_1 values for each tumour of between 0.0087-0.0526 s^{-1} were measured when breathing 100 % oxygen. This change was statistically significant in five lesions (Figure 1 and Table 1). The ΔR_1 returned to that of baseline on switching back to medical air in only one tumour (Pt 1 Tumour 2; p = 0.02). Group analysis showed clear elevation of ΔR_1 during oxygen inhalation ($p < 0.001$) and a non-significant reduction in ΔR_1 towards baseline values when patients returned to breathing medical air (p = 0.117) (Figure 2). Patient demographics and tumour details are summarised in Table 1. There was no significant correlation between the magnitude of oxygen-induced ΔR_1 and tumour median IAUC or K^{trans}.

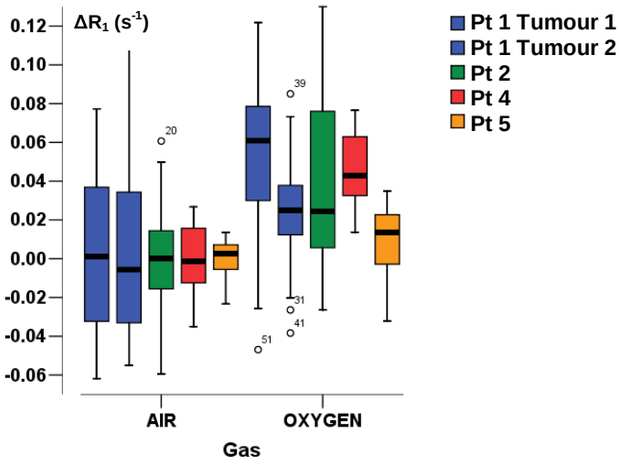

Figure 1 *Box-plot showing significant ΔR_1 in 4 patients (Pt 1 had two tumours). Outliers are represented by circles (○).*

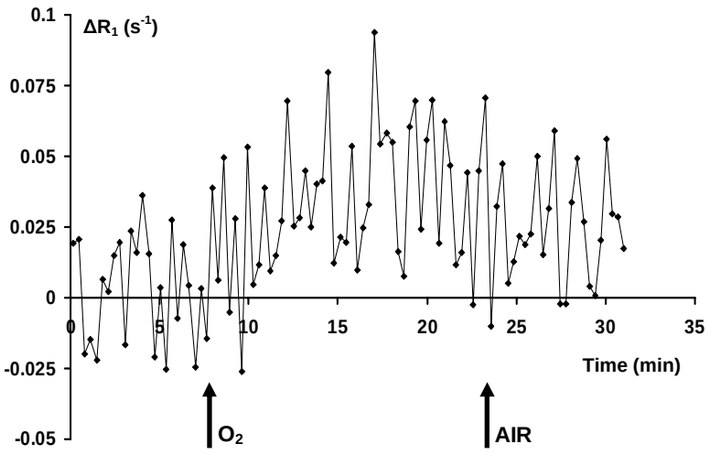

Figure 2 *Group averaged ΔR_1 in 5 patients with 7 tumours. Switch to breathing 100% oxygen (O_2) and medical air (Air) are indicated by arrows.*

Pt	Age	Tumour histology	Stage	Tumour site	Lesion	Previous therapy	Mean ΔR_1 air to O_2 (s^{-1})	95% CI (s^{-1})	p value
1	56	Clear cell ovarian carcinoma	IV	Liver	1	Cytotoxic CT	0.0526	0.0406 – 0.0646	<0.001
1	56	Clear cell ovarian carcinoma	IV	Liver	2	Cytotoxic CT	0.0259	0.0180 – 0.0337	0.006
2	80	Ovarian carcinosarcoma	IIc	Omentum	1	Cytotoxic CT	0.0463	0.0240 – 0.0686	0.004
3	73	Gastric adenocarcinoma	Metastatic	Liver	1	None	0.0101	-0.0187 – 0.0389	NS
3	73	Gastric adenocarcinoma	Metastatic	Liver	2	None	0.0238	-0.0023 – 0.0499	NS
4	51	Endometrioid ovarian cancer	II	Pelvis	1	RT/ Cytotoxic CT	0.0459	0.0404 – 0.0514	<0.001
5	52	Ovarian serous adenocarcinoma	IIIb	Pelvis	1	Cytotoxic CT	0.0087	0.0032 – 0.0142	0.003

Table 1 *Patient demographics and ΔR_1 on inhalation of 100 % oxygen. Mean ΔR_1 are displayed along with 95% confidence intervals and p values. Previous therapy included cytotoxic chemotherapy (CT) and radiotherapy (RT). NS = not significant.*

Discussion

This study is the first to describe oxygen-induced modulation of R_1 in human tumours. We report significant ΔR_1 when subjects switch from medical air to 100 % oxygen in four patients with advanced epithelial ovarian carcinomas. In addition, modest non-significant ΔR_1 were detected in two liver metastases in a patient with gastric adenocarcinoma. Our study shows that measuring oxygen-induced modulation of tumour R_1 is feasible. It can produce detectable signal change with an acceptable signal-to-noise ratio.

The image contrast exploited in this technique is due chiefly to the paramagnetic effect of dissolved molecular oxygen in arterial blood plasma and tissue fluid. Hence, arterial blood flow is likely to be an important factor contributing to signal change. However, measured ΔR_1 following oxygen inhalation was independent of the tumour blood flow estimated by both IAUC and K^{trans}, suggesting that oxygen-induced ΔR_1 is not simply a measure of flow. These preliminary results are encouraging and may provide novel MRI biomarkers of oxygenation status. The technique merits further investigation to test the hypothesis that the signal change is a composite measure of oxygen delivery, diffusion and metabolism.

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References [1]JL Tatum et al., (2006) Int J Radiat Biol 82: 699-757. [2]RA Jones et al., (2002) MRM 47: 728-35. [3]JP O'Connor et al., (2007) MRM 58: 490-6. [4]A Haase (1990) MRM 13: 77-89. [5]GJ Parker et al., (2006) MRM 56: 993-1000.