ConvectionMRI, a novel method for measuring tumour interstitial fluid velocity

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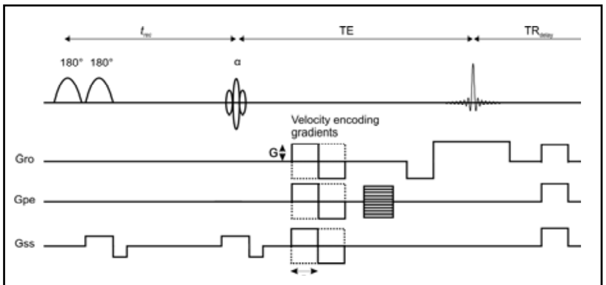

Figure 1: Timing diagram for the convectionMRI sequence.

Introduction: In this study, we present a novel technique named convectionMRI for non-invasively measuring tumour interstitial fluid velocity (IFV). Due to their high vascular permeability and poor vascular function, tumours exhibit raised interstitial fluid pressure (IFP), which has been shown in tumour xenograft models to be heterogeneously distributed, with high pressure in the centre and lower pressure towards the periphery [1]. This raised pressure impacts on drug delivery [2], is implicated in the development of metastasis [3] and induces a radial flow of fluid through the interstitium. It is proposed that convectionMRI can characterise and quantify IFV, a parameter of significant interest for characterising the tumour microenvironment and assessing barriers to drug delivery.

Methods and Materials: *ConvectionMRI:* The seqence is based on a velocity contrast sequence with a dual inversion recovery preparation (see Figure 1). A global adiabatic inversion pulse is administered, followed immediately by a slice selective inversion in order to recover the slice to equilibrium magnetisation [4]. Following a recovery delay t_{rec} in which inverted blood flowing into the selected slice recovers to the null point (t_{rec} = ln(2)$T_{1,blood}$), a gradient echo readout is applied, during which bipolar velocity encoding gradients are applied (G = 5 G/cm, τ = 20 ms). By nulling the vascular signal with the dual inversion, phase differences measured using standard velocity encoding techniques [5] should then reflect extra-vascular convection. The T_1 of blood ($T_{1,blood}$) was taken to be 1900 ms, as measured in the atrium of the mouse heart during a previous study, giving t_{rec} = 1317 ms. Velocity encoding required two repetitions of the sequence, the second of which used bipolar gradients of opposite polarity to the first. The difference in phase between the two measurements, $\Delta\phi$, is proportional to IFV. This measurement was performed in three directions, corresponding to phase, readout and slice-select imaging gradient orientations.

In vivo evaluation: MF1 nu/nu mice were injected subcutaneously on the lower right flank with 5×10^6 SW1222 or LS174T colorectal carcinoma cells. Tumours were allowed to grow to an average volume of 2.1 ± 0.5 cm^3 and were scanned using a 9.4T Agilent VNMRS scanner with a 39 mm birdcage coil (Rapid MR International, Columbus, Ohio). Mice were anaesthetised using isoflurane in O_2, and core body temperature was monitored and maintained at 37° using a warm air blower. Tumours were restrained using dental paste in order to minimise bulk motion. A single coronal slice covering the largest extent of each tumour was selected from a set of multi-slice, fast spin echo images, and was used to acquire convectionMRI data. The convectionMRI sequence included the following parameters: TR = 2500 ms, TE = 2.6 ms, flip angle = 30°, slice thickness = 1 mm, field of view = 35×35 mm^2, matrix size = 128×128. In order to evaluate the efficacy of vascular nulling, arterial spin labelling (ASL) data were acquired in the same slice and a reference, non-vascular nulled set of convectionMRI images (I_{total}) was also acquired using two global inversion pulses. Nulling ratio (NR, a measure of the efficiency of the vascular nulling module) was evaluated both in an agar phantom and *in vivo* as a function of assumed blood T_1, and was defined as NR = (I_{total} – I_{nulled}) / I_{total}.

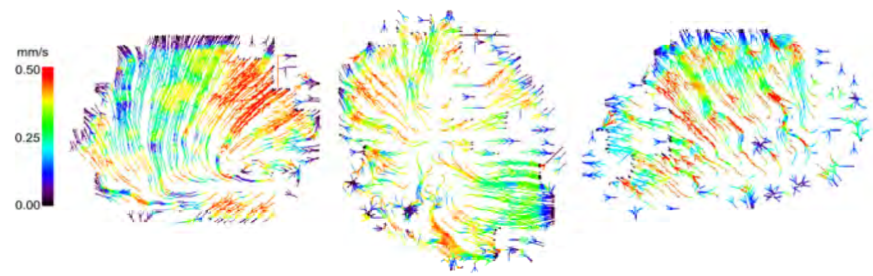

Figure 2: Streamline diagrams showing patterns of interstitial fluid velocity (IFV) within the tumour interstitium, acquired using the convectionMRI sequence.

Post-processing: The data were analysed using in-house software written in IDL. Fluid velocity was calculated using $v = \Delta\phi / (\gamma\, \Delta M_1)$ (where γ is the gyromagnetic ratio and ΔM_1 is the difference in first order velocity gradient moments). Maps of fluid velocity streamlines were calculated and visualised using the iVector tool in IDL.

Results: Figure 2 shows maps of fluid velocity streamlines from three tumour cross-sections. In these, and all other tumours studied, velocity profiles displayed a pattern of flow from a source within the tumour, towards the edge. This source was located either towards the centre of the tumour or at the lower edge, at the interface with the abdominal muscle wall. Streamlines were directed radially from the source, towards the outermost edge of the tumour. Median IFV was 0.28 ± 0.09 mm/s. Assessment of vascular nulling efficiency revealed effective nulling for $T_{1,blood}$ of between 1500 and 2100 ms (Fig. 3). Using a first-order estimate of blood volume v_B , median v_b was 9.69 ± 0.05 % for SW1222 tumours and 6.8 ± 0.1 % for LS174T, which is in good agreement with histological measurements [6].

Discussion: The results of this study demonstrate that convectionMRI, a novel imaging method, can reveal complex, macroscopic interstitial velocity patterns within the tumour interstitium that are consistent with those reported in the literature. We have shown that efficient vascular nulling can be achieved in tumour xenografts using inversion recovery preparation, allowing interstitial convection to be accurately probed with velocity encoding gradients. For the tumours studied here, measurements of nulling efficiency gave blood volume estimates that were of the order of those expected. The convectionMRI technique is arguably preferable to contrast agent-based approaches [7], due to their ability to directly quantify IFV vectors using endogenous contrast mechanisms. Methods for relating IFV to IFP are currently being developed and, potentially, convectionMRI will offer a practical, non-invasive technique for characterising this key feature of the tumour microenvironment and for assessing barriers to drug delivery.

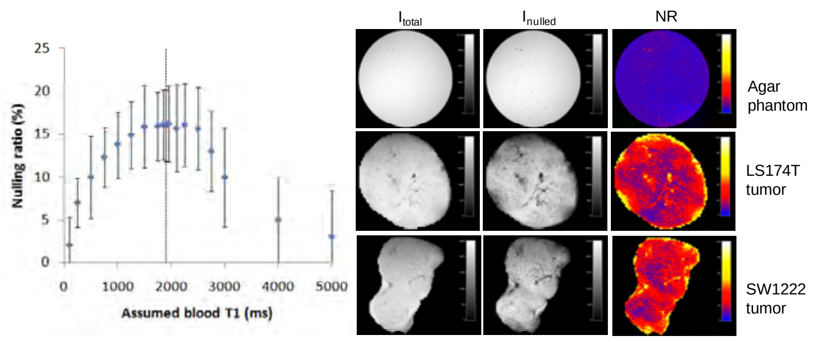

Figure 3. Efficiency of vascular nulling. Left: Nulling ratio (NR) as a function of assumed blood T_1 in a SW1222 tumour. Right: Images acquired without vascular nulling (I_{total}), with vascular nulling (I_{nulled}), and the NR calculated from these data, in an agar phantom and two tumour xenografts.

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