Direct Albumin Imaging in Mouse Tumour Model

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Introduction Here we present the *first example of direct protein imaging in a living animal*. *D*elta *r*elaxation *e*nhanced MR (dreMR) is a recent method that exploits the strong magnetic field dependence of slow-tumbling gadolinium-based contrast agents, especially about 1.5T[1,2]. The dreMR method allows one to directly differentiate MR image intensity due to bound contrast agent from all other sources of image intensity by dynamically changing the strengh of the applied magnetic field through the use a removable field-shifting insert coil.

Contrast from both unenhanced biological tissuse and tissue in the vicinity of fast-tumbling imaging probes, like GdDTPA, show little to no magnetic field dependence in the 1.5T range. Conversely, protein-bound probes like the FDA-approved contrast agent gadofosveset (MS-325, Ablavar) have a very strong field dependence with $\Delta r1=24.6\ mM^{-1}s^{-1}T^{-1}$ about 1.5T. By modulating the B0 field about 1.5T and taking T1-weighted images, the difference image gives signal solely attributable to the slow tumbling pool.[2]

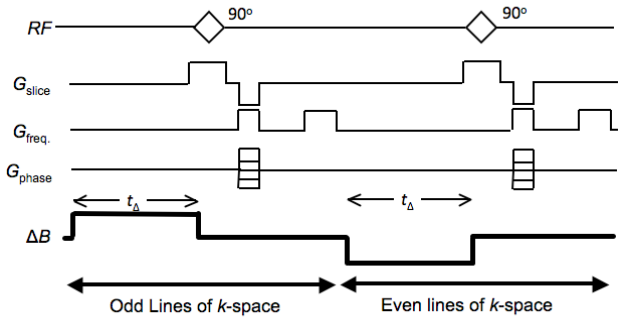

Fig 1. Field shifts are applied during the relaxation portion of the sequence. During acquisition the field is returned to its nominal value of 1.5T. Positive and negative pulses are interleaved. For the first image each odd line of k-space is field increasing and each even line is field decreasing. In the second image the order is reversed. The duration, labeled t_Δ of the field shift is variable from milliseconds to seconds. Switching is performed in 2.5ms.

Methods A 1.5T Siemens Avanto (Erlangen, Germany) was outfitted with an insertable, actively shielded electromagnet to dynamically control the magnetic field strength in the imaging region[1]. An athymic nude mouse implanted with two LS174T tumors was anesthetized with 1.5% isoflurane and placed on a heating pad inside a Tx/Rx birdcage RF coil within the dreMR electromagnetic insert coil. MS-325 (0.03mml/kg) was injected intravenously through the tail vein. For this study the magnetic field was varied from 1.4T to 1.6T to achieve the desired contrast. During image acquisition and RF excitation the magnetic field was returned to the nominal value of 1.5T. A modified gradient echo sequence was used with TR of 150 ms, TE of 5ms and 16 averages to obtain dreMR images. Magnetic field shifts of opposing polarity were provided for each line of k-space with the electromagnetic insert as shown in Fig. 1. The raw data was postprocessed in Matlab (Natick, USA) to obtain field dependence maps.

Results Fig. 2 shows conventional T1-weighted images (arrows point to tumors) prior to (Fig 2.A) and 5 min post (2.B) intravenous injection of MS-325. Post-Pre subtraction (2.C) demonstrates similar enhancement of tumor and muscle. The T1 difference image shows the effect of both free MS-325 and MS-325 bound to albumin. The dreMR image is only due to albumin-bound MS-325 and represents a direct image of the albumin distribution in the mouse. Interestingly, the dreMR image (2.D) shows different contrast than the T1 image. In the dreMR image (Fig 2.D&F) the tumors are more pronounced, presumably because of higher albumin levels in the tumors compared to the surrounding muscle. We also see differences in dreMR contrast within the different muscle regions that correlate with regions that are bright on T2w images (2.E) and suggest different albumin levels; we also see regions with essentially no dreMR contrast. The molecular origins of these contrast differences are being investigated.

Conclusion dreMR imaging is new form of MRI contrast that enables direct protein imaging in living animals.

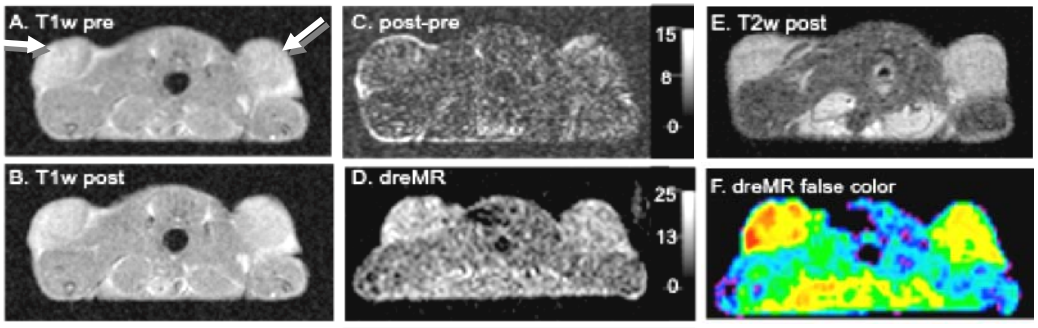

Fig 2. Mouse with two implanted tumors (arrows). T1w imaging pre- (A) and post (B) 0.03 mmol/kg MS-325, and (C) a subtraction of image A from image B to show the signal enhancement provided by MS-325. D) Shows dreMR SNR at full scale. E) T2 weighted image, TE=30ms. F) Albumin distribution map: dreMR image in false color with Gaussian blur to reduce noise.

References

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