Examining Tumor Microstructure with Temporal Diffusion Spectroscopy

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Introduction

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a noninvasive imaging technique commonly used to quantify the apparent rate of water diffusion within biological tissues. The apparent diffusion coefficient (ADC) in tissues reflects the influence of cellular membranes and other structures that serve to hinder the molecular motion. Consequently, measurements of ADC using appropriate pulse sequences may be made sensitive to the density of restrictive barriers within the local environment and, therefore, may be used as a probe of tissue microstructure. Such techniques have gained widespread attention for their potential ability to characterize tumor proliferation and treatment response (1-2). However, current approaches probe the reduction in ADC at specific, relatively long diffusion intervals, which correspond to specific spatial scales. Consequently, these methods are less sensitive to changes within tissues that occur on much finer spatial scales.

The conventional method used to measure ADC is the bipolar pulsed gradient spin echo (PGSE) technique, which measures water displacement over a diffusion time interval which is typically on the order of tens of milliseconds. During this time, a diffusing water molecule should diffuse approximately 5 – 15 microns, so that in this time it will likely encounter one or more cell membranes and experience a multitude of restrictive barriers. The measured ADC will reflect the aggregate of all such interactions across the entire sample, obscuring details of structure on smaller scales. If the diffusion time were to be much shorter (order of 1 millisecond) the diffusion distance would be similar to or less than a cell diameter, so that variations in ADC would be more sensitive to changes in intracellular structure. Oscillating gradient spin echo (OGSE) techniques examine diffusion over such short effective time scales and can, therefore, be used to probe such microscopic dimensions. These techniques, which have been described previously (3-4), reveal details of tissue microstructure that would otherwise be obscured with conventional methods, a result that may be of particular importance when examining the response of a tumor to specified treatments.

Methods and Results

We have applied both OGSE and PGSE methods at 4.7T to measure the ADC in male Wistar rats 14 days after innoculation with C6 gliosarcoma cells. Diffusion-weighted PGSE measurements were obtained with δ = 3 ms, Δ = 15 ms, and b = 401 s/mm^2, while OGSE measurements were collected, at the same b-value, by varying the oscillating gradient frequency between 30Hz and 240Hz, corresponding to effective diffusion times between 16.7 ms and 2.1 ms, respectively. Other imaging parameters were TR/TE = 2000/76 ms, FOV = 36 mm x 36 mm, matrix = 64x64, slice thickness = 2 mm. Representative ADC maps for both techniques are shown in **Figure 1**. As demonstrated, the ADC map obtained with OGSE methods at 240 Hz, panel (d), is significantly different from that obtained at lower frequency, panel (c) at 30 Hz, or with PGSE, panel (b). The increased contrast stems from the ability of OGSE methods to measure diffusion over much shorter spatial scales, revealing a greater range of restrictions within the inhomogeneous structure of the C6 tumor.

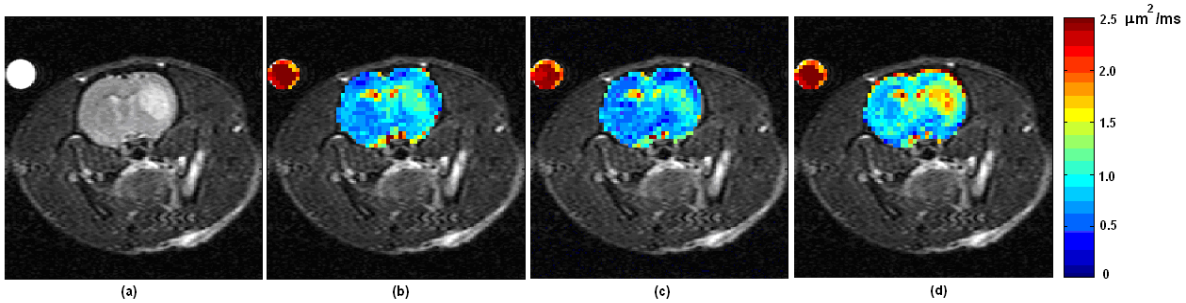

Figure 1. T2-weighted image of C6 gliosarcoma and ADC maps obtained with PGSE and OGSE methods. (a) T2-weighted image. (b) ADC map obtained with PGSE. (c) ADC map obtained with OGSE (30 Hz). (d) ADC map obtained with OGSE (240 Hz).

Figure 2 further demonstrates the effect that short diffusion times have on the measured ADC. For a set of voxels within a whole tumor region of interest, for one representative animal, a scatter plot of ADC values obtained with PGSE are compared to those values obtained with OGSE at three different oscillation frequencies (30Hz, 150 Hz, and 240 Hz). As this figure illustrates, the ADC increases with increasing frequency (decreased diffusion time), while measurements in free, unrestricted water remain consistent between the methods, as expected. The significance of this result is that the measurement of ADC using OGSE techniques provides a broader range of contrast in corresponding ADC maps.

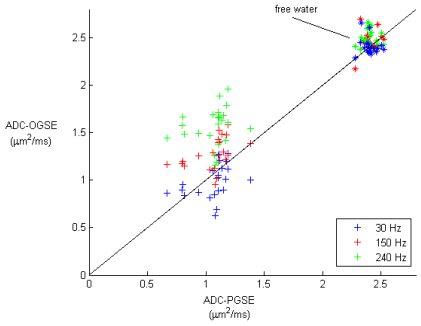

Figure 2. Scatter plot of ADCs obtained within a whole tumor region of interest. Abscissa represent values obtained via PGSE, while ordinates represent values obtained via OGSE (30 Hz, 150 Hz, and 240 Hz). Values for free water are also shown.

Discussion

Using the OGSE technique, we have been able to assess water displacements over only a few microns within a tumor environment. Our measurements and analysis show there were statistically significant differences in ADC obtained by OGSE methods at moderate to high frequencies (equivalent to short diffusion intervals) compared to conventional PGSE methods, and these differences varied for different tissues. The broader range of ADC values at higher frequencies produces greater contrast in the corresponding parametric ADC maps, and provides details of the tumor microenvironment that are obscured by conventional PGSE techniques. The ability to resolve such details of tumor microstructure may prove beneficial in evaluating the efficacy of therapeutic treatments at their earliest stage, and are the focus of ongoing studies.

References

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