

MR Signal Fluctuations and Tumor Vasomotion

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INTRODUCTION

Fluctuations in MR signal intensity of the resting brain is believed to be related to vasoconstrictive physiological motion; such fluctuations occur at a frequency far lower than cardiac and respiratory motion. This vasomotion has been found to be regionally synchronized (e.g., visual and motor cortices), and may also relate to disease [1,2]. In this study we extend the analysis of low-frequency vasomotion, centered at 0.1-Hz, to brain tumors (glioblastoma multiforme, or GBM), and examine how such vasomotion evolves under anti-angiogenesis therapy.

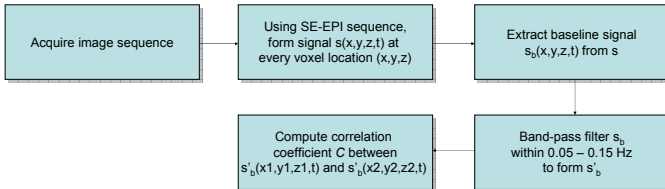
HYPOTHESIS

Tumors create abnormal vasculature which are leaky, disorganized, tortuous, dilated, and haphazard [3]. Anti-angiogenesis therapies have been found to normalize this vasculature [3,4]. Due to this state of disorganization, we hypothesize that there is decreased synchronous vasomotion in tumors. We further hypothesize that normalization of the tumor vasculature will increase the amount of synchronous vasomotion.

SUBJECTS AND METHODS

Data and Subjects. Subjects with GBM undergoing anti-angiogenesis therapy using the drug AZD-2171 are scanned using a Siemens 3-T MRI (Tim Trio, Siemens Medical Solutions, Malvern, PA). A subset of 10 patients were randomly chosen from a larger study population; mean and median ages of the subgroup are 53.1 and 54.5 years, respectively. Patients were scanned twice (day -5 and -1) at baseline, and began receiving oral doses of AZD-2171 on day 0. Additional imaging scans were performed while the subjects remained on study, at days +1, +28, and sometimes +56. Dynamic susceptibility contrast (DSC) imaging is performed – a 75-mm slab of tissue is imaged using a dual-echo, combined gradient-echo and spin-echo echo planar sequence. Such a sequence permits the acquisition of two images after each 90-deg RF excitation: a gradient-echo image (TE: 34) and a spin-echo (SE) image (TE: 103). Each image is acquired 1.33-s apart, and has an in-plane resolution of 1.7-mm and through-plane resolution of 5-mm, producing a 128x128 matrix. Gd-DTPA is injected after 85-sec of imaging, providing 63 baseline resting-state images for vasomotion analysis. Additional channels of data, including pre- and post-contrast T1 and MPRAGE, are also acquired. Study was performed in accordance with IRB-approved protocols.

Processing. Vasomotion data is processed as follows:



The correlation coefficient C between signals s and r is defined by

$$C(s, r) = \frac{n \sum s_i r_i - \sum s_i \sum r_i}{\sqrt{n \sum s_i^2 - (\sum s_i)^2} \sqrt{n \sum r_i^2 - (\sum r_i)^2}}$$

Two types of vasomotion correlation images are created:

- Seed-based, where a voxel is chosen as the template (seed), and the correlation coefficient of every voxel relative to the seed is computed. This is used only for the image of the visual cortex to confirm our approach.
- Neighborhood-based, where the value of a voxel is the average with its two neighboring voxels (above and left):

$$C_{avg}(x_i, y_j, z_0) = \frac{1}{2} \{ C(s_b(x_i, y_j, z_0), s_b(x_{i-1}, y_j, z_0)) + C(s_b(x_i, y_j, z_0), s_b(x_i, y_{j-1}, z_0)) \}$$

All vasomotion images of tumors are created using this method to convey regional synchronicity.

RESULTS

Confirmation of Approach. To confirm that the technique developed properly captures vasomotion, a voxel from the visual cortex is selected and correlated with all voxels in the image (Figure 1). The resulting region of high correlations is consistent with what has been reported in the literature and identifies the visual cortex.

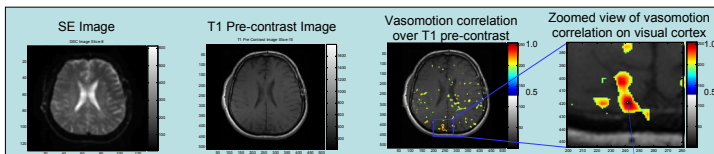


Figure 1. Confirmation of vasomotion detection approach using visual cortex. Vasomotion computed using SE image sequence at resting state over 84-sec. Colormap overlay displaying correlations within the range of [0.5 – 1.0]. Seed voxel correlated more strongly with voxels within the visual cortex than any other region of the brain.

Tumor Vasomotion. Data from 10 subjects were selected for vasomotion analysis (see Figure 2). For each subject, registered spin echo, T1 post-contrast, and MPRAGE images are identified. On the basis of the SE image, neighborhood correlations of the vasomotion data were performed. Regions of very high degrees of synchronous vasomotion ($C > 0.85$) are overlaid on the MPRAGE images. Highly synchronous regions within the tumor can be seen.

ACKNOWLEDGEMENT

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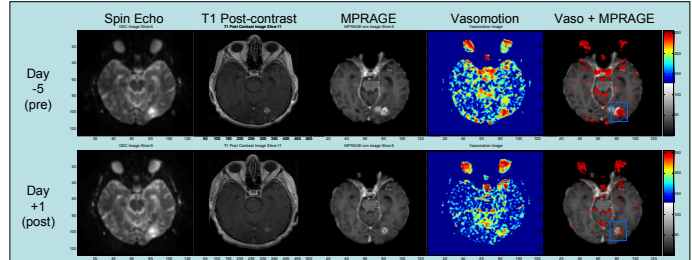


Figure 2. Pre- and post-therapy SE, T1 post-contrast, MPRAGE, vasomotion, and vasomotion-MPRAGE overlay images. The vasomotion image displays neighborhood correlation values within the range of [0.5 – 1.0]. Color overlays of vasomotion correlation displays only regions of high correlations (> 0.85). Note the reduction in the tumor vasomotion (blue box) after commencement of the anti-angiogenesis therapy.

RESULTS (con't)

Tumor Vasomotion and Drug Therapy. We examined tumor vasomotion response to AZD-2171 over time in 10 patients. Specifically, the following procedure was used:

- The tumor at day -1 was outlined by a neuroradiologist; this outline defines the region of interest (ROI).
- Every dataset is registered to that of day -1 so that the same ROI is used.
- The degree to which each dataset contained high tumor vasomotion is tabulated by integrating high correlation coefficients ($C > 0.85$) voxels within the ROI, and subsequently normalizing by the volume of the ROI.
- For each subject, this normalized sum is further normalized by that of day -1 so that variations relative to day -1 are easily discernable.

Note that the vasomotion content of highly synchronous voxels is computed in 3-D so as to minimize the effect of head orientation variations from one visit to the next. The result of this analysis is shown in Figure 3. Although not shown, we note for completeness that each patient's response to therapy was evaluated by a neuroradiologist and designated as progressive disease, stable disease, or partial response; we did not observe any correlations between raw vasomotion values, relative values, changes over time, versus the patient's response designation.

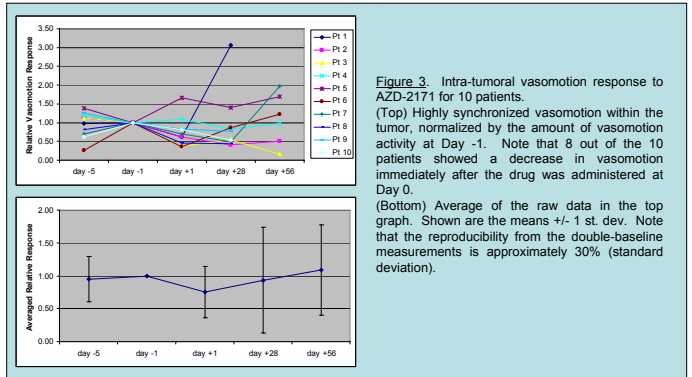


Figure 3. Intra-tumoral vasomotion response to AZD-2171 for 10 patients.

(Top) Highly synchronized vasomotion within the tumor, normalized by the amount of vasomotion activity at Day -1. Note that 8 out of the 10 patients showed a decrease in vasomotion immediately after the drug was administered at Day 0.

(Bottom) Average of the raw data in the top graph. Shown are the means +/- 1 st. dev. Note that the reproducibility of the double-baseline measurements is approximately 30% (standard deviation).

CONCLUSIONS AND DISCUSSIONS

The following observations can be made about using vasomotion to analyze tumors, as well as the impact of anti-angiogenesis therapy:

- There appears to be a higher level of synchronous vasomotion in tumors (GBMs).
- A majority of the patients exhibited a drop in vasomotion following the first dose of AZD-2171.
- Measurement reproducibility is approximately 30% standard deviation.

Overall, the analysis of vasomotion yielded interesting results, although neither the physiological mechanism nor the prognostic value of vasomotion measurements, as they relate to tumor therapies, are well understood. Vasomotion measurements as described here are noisy – a neighborhood function incorporating more voxels than the 2 immediate neighbors may yield smoother results. Lastly, it is interesting to note that, in a purely computational study, it was shown that vasomotion increases oxygen transport in capillary networks [5], potentially providing an explanation of why tumors appear to exhibit a greater degree of vasomotion.

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