Tumor Angiogenesis and Vasculature MRI with Endogenous BOLD Effect

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Introduction

Angiogenesis is a normal physiological process by which new blood vessels grow from pre-existing vessels. Fundamentally, angiogenesis plays a key role in the growth and development of new tissues. In the case of a tumor, however, angiogenesis becomes the primary facilitator of rapid tumor growth and metastasis. As a result, angiogenesis inhibition has become an area of increased focus for researchers and pharmaceutical companies seeking to develop new methods of cancer treatment. Traditionally, the gold-standard technique to quantify tumor vasculature has been the histological estimate of microvascular density (MVD). This method, however, is inherently invasive, time consuming, and suffers from sampling bias. To overcome these limitations, researchers turned to MR tumor vasculature imaging. Some of the most successful reported techniques such as Dynamic Contrast Enhanced (DCE) MRI employ exogenous contrast agents. Methods based on the endogenous contrast, such as Arterial Spin Labeling (ASL) and Blood Oxygen Level Dependent (BOLD) MRI induced by carbogen/hyperoxic challenges were also investigated. These methods, however, do not provide sufficient sensitivity for high-resolution imaging of tumor vasculature. In this work, we hypothesize that carefully induced hypoxia can exhibit previously undetected high levels of endogenous BOLD contrast that can be used to generate high-resolution tumor vasculature MR maps.

Methods

Rats with tumors (9L glioma, 4-6 weeks post tumor implantation, n=4) were anesthetized with isoflurane (1.5% maintenance) and imaged in a 9.4T horizontal bore small animal scanner and with 35-mm diameter commercial quadrature proton coil. During the imaging procedure, rat body temperature was maintained with heated air while T_2*-weighted gradient echo images (TR=0.5s and TE=10ms) were acquired from rat brains under different levels of oxygenation inhalation. Oxygen was administered in four concentrations (hypoxia 8%, 15%, normoxia 21%, and hyperoxia 100%) along with diluted N_2 at a fixed flow rate of 35 cc/min. BOLD contrast maps, correlating to vessel density, were calculated by normalizing subtraction images with same slice normoxic images. Additionally, 3D imaging of tumor vascular was done with a multi-slice gradient echo sequence (number of slice=20, slice thickness=0.5mm). Overall, total imaging time was approximately 4 minutes at each type of inhalation. All animal procedures were performed under an approved institutional animal care and use committee protocol.

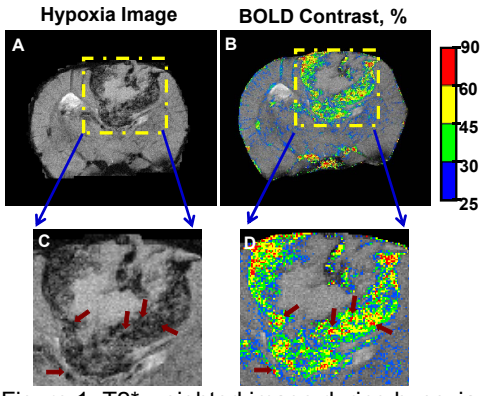

Figure 1. T2* weighted image during hypoxia (8% O_2, A or C) shows hypointensive region at the boundary of brain tumor due to the tumor vasculature, which is not visible from normoxia and hyperoxia images. Color-mapped BOLD contrast map (B or D) allows us to identify individual vessels (arrows in D) in the tumor periphery and potentially quantify tumor vessel density.

Results

Overall, hypoxic inhalation induced much higher BOLD contrast in tumor vasculature than hyperoxic inhalation compared to normoxic condition. Specifically, the signal from tumor vasculature decreased greatly at 8% O_2, and resulted in a hypo-intensive circle around tumor periphery while having minimal influence on normal brain and non-vascularized tumor tissue. Quantitatively, hypoxia induced an average contrast ~40% from tumor vasculature, and permitted the acquisition of high resolution imaging of tumor vasculature. Figure 1 shows a high-resolution BOLD contrast map, acquired in ~ 4 minutes, in which some individual vessels can be identified and regional vessel density can be observed. Figure 2 demonstrates a MIP (maximum intensity projection) BOLD contrast map constructed from 20 slices. Tumor vasculature, its origins and metastasis are clearly visible.

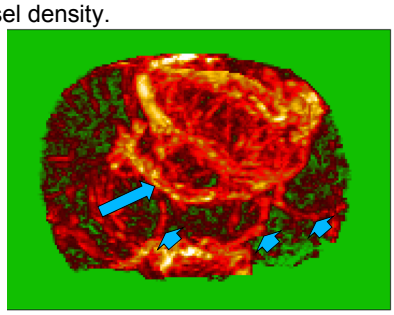

Figure 2. MIP (maximum intensity projection) image of tumor vasculature generated from multi-slice vessel density images clearly shows tumor vasculature, its origins (arrow heads) and tumor metastasis (arrow).

Conclusion

Since previously conducted studies of tumor angiogenesis and vasculature with BOLD MRI were unsuccessful in generating sufficient contrast for high resolution imaging, this study sought to overcome this limitation by using a hypoxic challenge to generate BOLD contrast. Overall, this technique produced sufficient contrast (~40%), with which high-resolution tumor vasculature maps were obtained. Additionally, the short imaging protocols used in this experiment permitted 3D high-resolution tumor vasculature maps to be acquired in minutes. From a diagnostic perspective, this technique allows us to quantify tumor size, measure tumor vasculature density, provide early detection of tumor metastasis, monitor the effectiveness of cancer treatment drugs, and could potentially characterize tumor grade and aggressiveness. This method might even provide a non-invasive substitute for histological methods of quantification of vessel density. Furthermore, while the preliminary data from this study has verified the ability of this novel technique to image tumor angiogenesis and vasculature, histological staining is being conducted to confirm the vessel density maps and to provide a further correlation between quantified MVD and the BOLD contrast maps obtained with this technique. Longitudinal studies on tumor progression associated with anti-angiogenesis treatments are also under study.

Acknowledgement

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