Vascular Fingerprinting in Rat Brain Tumors

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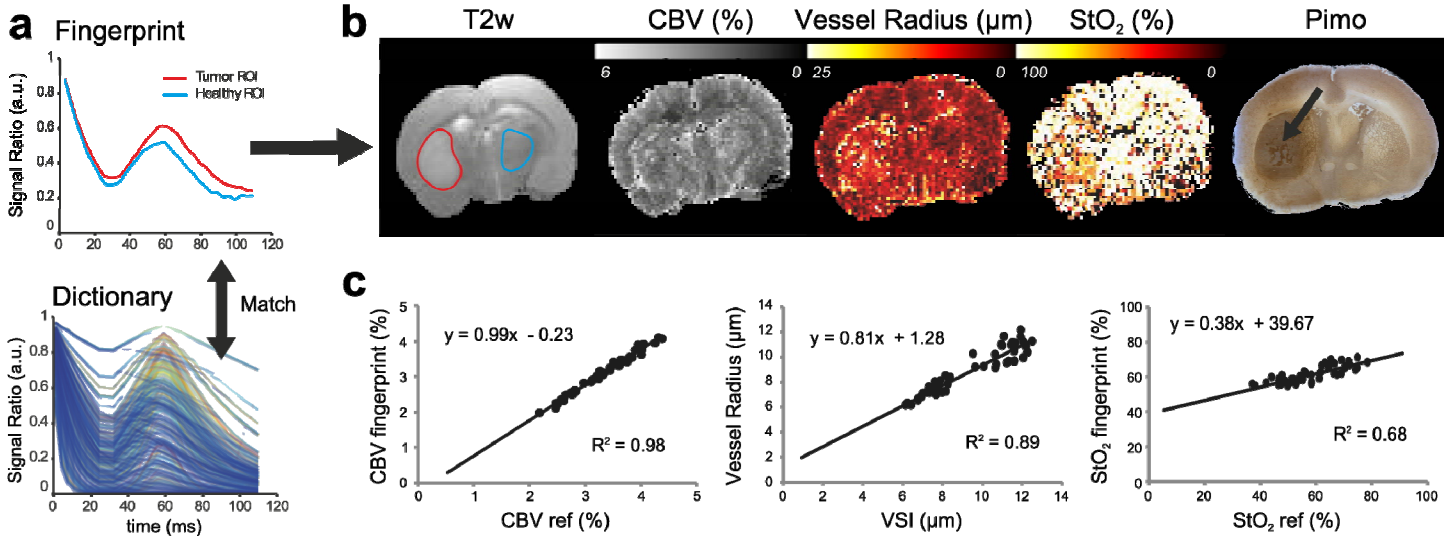
Introduction: Microvascular characteristics are potentially important biomarkers for studying angiogenesis or hypoxic processes in pathologies such as cancer or stroke. Based on the concept of MR fingerprinting [1], a recent MRI approach has been proposed to extract microvascular properties from *in vivo* acquisitions, and could offer high resolution mapping of blood volume fraction, blood vessels geometry, and blood oxygenation [2]. In 'MR vascular fingerprinting', the MR signal evolution (Free Induction Decay + Spin echo=fingerprint) is sampled in every voxels and is compared to a dictionary of curves obtained using advanced numerical simulations of the same experiment. Encouraging results have been obtained in normal human volunteers with numerical values and spatial patterns in line with previous literature reports. In this study, we tested the vascular fingerprinting approach in a pathological condition (8 rats bearing brain tumors) and compared the results to more conventional MR methods: steady-state susceptibility contrast imaging for blood volume (CBV), Vessel Size imaging (VSI) and quantitative BOLD imaging for blood oxygen saturation measurements (StO_2). In two rats, high spatial resolution/SNR maps were obtained and compared to pimonidazole staining, a histological marker of tissue hypoxia.

Materials and Methods: The local IRB committee approved all studies. Imaging was performed on a 4.7T Bruker system. 9L tumors were implanted in 8 rats and imaging was performed 13 days after. The MRI protocol included a T2-weighted spin echo sequence used to acquire structural information of the whole brain, a diffusion weighted EPI sequence used for Apparent Diffusion Coefficient (ADC) mapping and multiple spin/gradient echo sequences for relaxometry (T2 and T2*) mapping. A Gradient Echo Sampling of the FID and Spin Echo (GESFIDE) sequence (TR=4000 ms, 32 echoes, SE=60ms, 5 slices, 1 NEX, voxel size = 234x234x800µm^3, Tacq=6min and 24sec) was acquired pre- and post-injection of USPIO (P904, Guerbet, France, 200µmol Fe/kg). The fingerprints were created as the ratio (Signal Ratio) of the two GESFIDE acquisitions obtained pre and post injection to remove effects of B0 and T2 [2]. The dictionary was created using 'Numvox' [3], a numerical simulation tool that uses a Fourier based approach to compute the magnetic field distribution inside a virtual voxel and a deterministic approach to account for relaxation and diffusion processes. For sake of simplicity, straight cylinders were used here as blood vessels. 98000 individual simulations were performed to compute the dictionary by changing blood volume CBV=[0.5:25] %, blood vessel radius R=[1:25] µm and blood oxygen saturation StO_2=[0:100] %. To processing MRI data, fingerprints (i.e. Signal Ratio) and dictionary were eventually compared using least square minimization. In two rats, spatial resolution was increased to 234x234x600µm^3, the number of averages was set to 3, and animals were injected with pimonidazole 1 hour before the MR imaging session and sacrificed right after for histology analysis. Reference CBV and VSI were computed using the classic approach described in [4] and reference StO_2 using the method described in [5], a method which combines T2*, T2 and blood volume estimates.



Results: Fig.1a shows fingerprints obtained in healthy tissue and tumor regions in one rat. The temporal evolutions are distinct from each other but the global shapes are similar to the curves in the dictionary. Fig.1b shows high resolution parametric maps obtained in one rat. Variations of the microvascular parameters can be seen in the lesion environment (red ROI). The blood oxygenation map shows lower values in the tumor region (StO_2=64±2%) compared to the contralateral hemisphere (StO_2=73±0.2%). This is in good agreement with the presence of hypoxic regions reported with pimonidazole staining. Yet, the global values seem too high in regards to previous reports obtained with PET [6] and several voxels present saturated values. The comparison with other MR measurements is summarized in the form of scatter plots in Fig. 1c. A very good correlation is found between CBV measurements (R^2=0.98, slope close to unity). Vessel Radius measurements are also well correlated to VSI (R^2=0.90). The slope of the relation (0.81) can be explained by the fact that VSI does not exactly correspond to the averaged vessel diameter in the voxel [4]. Blood oxygenation measurements obtained with vascular fingerprinting are in line with multiparametric qBOLD imaging (R^2=0.68), but the range of values is clearly lower in the fingerprinting approach.

Conclusion: This study suggests that quantitative maps of microvascular parameters can be obtained with the vascular fingerprinting approach in rat brain tumors. The results are in good agreement with other MRI measurements but the proposed approach provides more flexibility. For example, virtual voxels that take into account the angiogenesis process could be created. Magnitude, phase or other MR sequences could also be combined to offer new dimensions to the dictionary (provided that each fingerprint is unique and that SNR is sufficient to allow the distinction between two fingerprints). The MRI protocol could be optimized by evaluating the influence of the spin echo time, number of echoes, contrast agent dosage and SNR. This optimization should further improve the accuracy of StO_2 measurements.

References: [1] Ma et al., Nature 2013. [2] Christen et al., ISMRM 2013 #451. [3] Pannetier et al, Plos One 2013. [4] Tropres et al., MRM 2001. [5] Christen et al, NMR Biomed, 2011. [6] Leenders et al, Brain, 1990.