Echo-based Single Point Imaging: A Novel Pulsed EPR Imaging Modality for High Spatial and Spectral Resolution for in vivo Quantitative Oximetry

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Introduction: EPR imaging is a new in vivo tool for the quantitative estimation of tumor hypoxia that help in treatment planning and the assessment of treatment outcome in small animal tumor models. Combined with MRI co-registration this technique may hold important clues as models for for effective management of tumor treatment by radiation as well as chemotherapy. We describe in this work our new approach to in vivo tumor imaging and quantitative oximetry in selected tumor mouse models.

Method: Low frequency time-domain EPR imaging in the frequency range 250-300 MHz has been found to be suitable for in vivo imaging in terms of an optimum compromise between tissue penetration and detection efficiency. Two main approaches are currently in vogue for time-domain spectroscopic EPR imaging. The first one is multi-gradient Single Point Imaging involving global phase encoding. One gets high resolution images, where the oximetry, however, is a T_2* based approach relying on apparent line width evaluations which may be subject to susceptibility effects and therefore needs system-dependent line width calibrations.[1] The second approach for EPR oximetric imaging utilizes the conventional 90°-τ -180° Spin-Echo pulse sequence well-known in MRI, and the images are obtained by the filtered back-projection after FT of the echoes collected under frequency-encoding gradients.[2] The spatially resolved oximetry information is derived from a set of T_2-weighted images as a function of the echo time 2τ. The back-projection images suffer susceptibility artifacts with resolution determined by T_2*, although the decay constant of each pixel follows the intrinsic T_2, leading to oxygen concentrations that needs only a one-time calibration of line width versus T_2. A novel time-domain spectroscopic EPR imaging approach, that is a unique combination of the above-mentioned techniques, is presented here.[3] The current approach combines Single Point Imaging with the Spin-Echo signal detection procedure to take advantage of T_2 (and not T_2*) dependent contrast and the enhanced spatial resolution associated with the constant-time pure phase-encoding approach. This approach has become feasible because of the availability of non-toxic water-soluble trityl and deuterated trityl based spin probes which have T1 and T_2 in the range 5-10 μs.

Instrumentation & results: Our pulsed EPR spectrometer used for single point imaging has been upgraded with a home-built pulse programmer that is capable of providing a three pulse sequence, for example 90-τ-180-τ-180 so that one can generate an FID and two echoes. By a suitable choice of time points in the time domain signal it is easy to pick at least five time points at which the net phase encoding remains identical leading to several sets of T_2-weighted images of identical FOV, enabling accurate spatially resolved T_2 which, in turn leads to quantitative 3D mapping of oxygen in tumor tissues.(Fig.1&2) This approach is faster than our current multi-gradient single point imaging time-wise, and generates high resolution images characteristic of the pure-phase encoding approach and leads to quantitative oximetry based on intrinsic T_2 and not T_2*. It is not necessary to have two refocusing pulses. One will also do. Oxygen dependent T_2 leads to quantitative oximetry in phantoms and in vivo (Figs. 3).

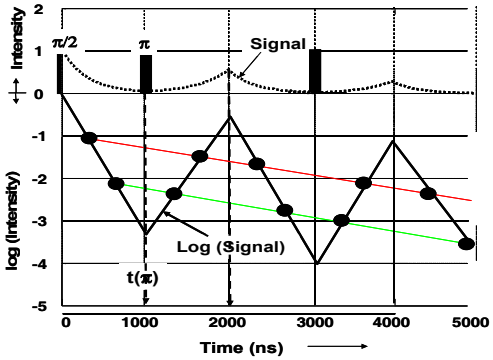

Fig.1 Schematics of Echo based SPI. Simulation shows that the FID intensities at time points denoted by ● are governed by true T_2. At these five time points, contribution from T_2* and field inhomogeneity & susceptibility cancel.

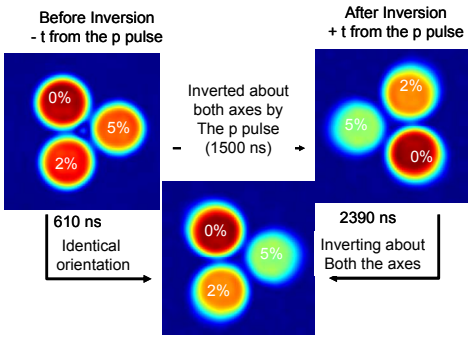

Fig.2 T_2-weighted pair images of a three-tube phantom processed by SPI at time time points (for a 90-t-180 two-pulse echo sequence) The iamge from the time point post 180 deg pulse is inverted along boith axes and has to be reinverted for T_2 evaluation

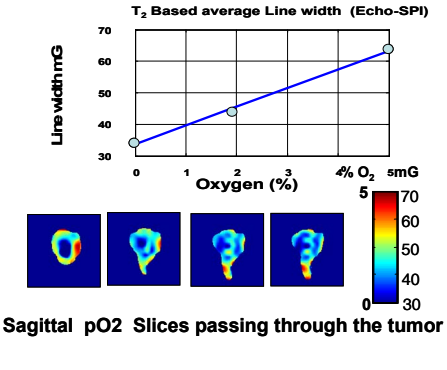

Fig.3 *Top:* The linearity of oxygen relaxivity in terms of mG of line width versus % of oxygen from phantoms. *Bottom:* In vivo oximetry on SCC mouse tumor showing mm slices through the tumor and the map of oxygen distribution

Reference: (1) E. D. Barth et al. *Magn. Reson. Med.* 2003. **49**(4): p. 682-691. (2) K. Matsumoto et al. *Magn. Reson. Med.* **55** (5): 1157-1163 (2006) (3)S. Subramanian et al. Pulsed Time-Domain Electron Paramagnetic Resonance: In Vivo Tissue Oxygen Imaging Via Cooperative ESE/ESPI - US Patent app. # 61/200,579.