Time-domain Spectral Spatial RF EPR Imaging

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Synopsis

Single Point or Constant Time imaging (SPI or CTI) technique, which is a pure phase-encoding methodology, leads to images of superior quality, compared to filtered back projection, in time domain EPR imaging [1]. This is because the image processed from a single time point after a specific delay from the pulse has no spectral information. However, the line width information manifested through the T_2* can be evaluated from a series of sequential single point images generated from the same experiment. EPR imaging in the SPI modality and can provide images of pO_2 distribution in vivo in a quantitative manner.

In vivo Oxymetry using EPR imaging necessitates the estimation of spatial distribution of paramagnetic spin probes co-registered with their spectral information. One approach is to perform spectral spatial imaging, especially in CW EPR by collecting images with space and spectral encoding gradients and employing filtered back-projection (FBP) for image reconstruction. For a given spatial axis, there is an orthogonal 'pseudo axis' corresponding to the spectral dimension. The so-called spectral 'viewing angle' depends on the relative magnitudes of spectral axis and spatial axes. Viewing angles close to 90° need very large field gradients, which are not attainable in practice leading to problems of 'missing angle-projections'. We have developed time-domain EPR imaging of small animals using pulse techniques at 300 MHz using spin probes with narrow line width. Employing SPI, and using maximum gradients of about 1 G/cm, we are able to generate spatial images with mm resolution. The use of Cartesian rastering for phase encoding enables direct Fourier reconstruction, eliminating any filter influence that generally leads to the well-known 'star-artifacts' in the conventional filtered back-projection method of reconstruction with limited projections. However, in SPI experiments, the spectral information can be recovered by considering the complete sequence of single points that can be easily acquired in the same acquisition. Since the field of view (FOV) is an inverse function of the time-delay from the pulse, it is necessary to resize the series of images to common FOV by accurate interpolation and perform an additional Fourier transformation along the time axis to generate pixel-wise or voxel-wise spectral information, simulating the spectral/spatial modality. There are no 'missing-angle' problems to deal with in this modality compared to the FBP method. The T_2* that is derived from such a process can be used to provide local in vivo oxygen concentrations in a non-invasive way, since the relaxivity of oxygen on the TAM radicals has been found to be a linear function of pO_2 from 0-160 mm of Hg. Results from oxygen phantoms and quantitative tumor hypoxia measurements in mice are presented. Breathing of oxygen-rich gases (such as Carbogen, 95% O_2, 5% CO_2) leads to re-oxygenation of tumor (data not shown). Since T_2* based oxymetry deals with the quantification of pO_2 based on the broadening of the lines, we employ fiducials of known oxygen concentration as internal, *in situ* reference standards. Time domain CTSSI, as we call this procedure, is faster than CW spectral spatial imaging and would be a useful technique when the pharmacokinetics of the spin probe is too fast and likely to cause concentration changes during the measurement. Overall, EPR in the SPI modality provides spatial distribution of the paramagnetic agent at useful spatial and temporal resolution with the pO_2 dependent spectral information co-registered

Materials and methods

We have designed and constructed a time domain EPR spectrometer/imager operating at 300 MHz. and the spectrometer schematics and Single Point imaging modality has been described previously [2]. For imaging the legs of a C3H mouse, a 25 x 25 mm resonator was used and 121 (11 x 11) phase-encoding steps were performed. About 1 mmol per kg body weight of TAM probe was administered intravenously (*via* tail vein cannulation) to produce a series of 6 to 8 time-course images. The spectrometer schematics, operation, data collection and image processing were automated using C^{++} and Matlab® programming on a PC platform [3].

Results & Discussion

The TAM spin probes which have line widths in the absence of oxygen on the order of 200 mG (which includes unresolved hyperfine coupling) have *apparent* transverse relaxation times around 1 µs and the gradient-free FIDs resulting from an impulse response lasts for about 3 µs. Since the phase or frequency encoding gradients impart additional shortening of the relaxation time T_2* the conventional method of collecting the FIDs under constant gradients and obtaining the projections by Fourier transform followed by the reconstruction of the images by filtered back projection is fraught with artifacts caused by gradient dependent sensitivity. Large gradients to obtain higher resolution often lead to unacceptable loss in sensitivity and image distortion. This is because of the T_2* dependent differential loss of signals during the dead time. The SPI modality, on the other hand produces linewidth-independent images [3]. The T_2* information is recovered by rescaling the images to a common field of view and performing a pixel-wise or voxel-wise FT along the axis of time-delay from the pulse. Results from phantoms and mice tumors show that the SPI modality can be performed to yield spectral spatial information and hence to functional / physiological imaging. The spectral information can lead to in vivo quantitative oxymetry. The schematic of generating spectral spatial data is illustrated in Fig.1. Results of 2D SPI oxymetry on phantoms and C3H mouse leg SCC tumors are illustrated in Fig.2 & 3.

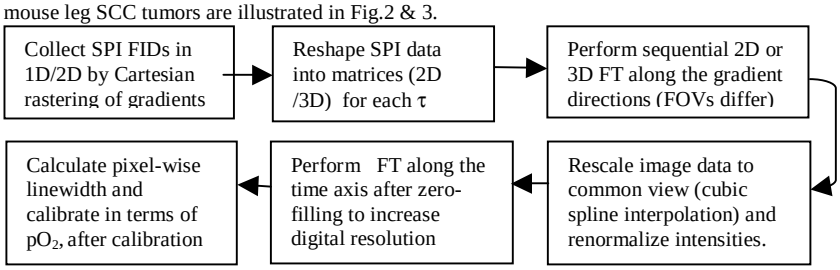

Fig.1. Schematics of data collection and analysis to yield spectral/spatial information from SPI data. Since the data are collected with a high-speed digitizer in presence of phase-encoding gradients, several hundred single points for sequentially delayed values of τ are collected in the same experiment.

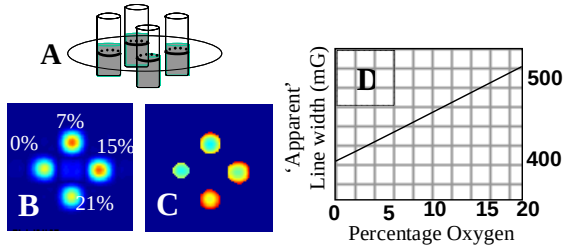

Fig.2 (A) A 4-tube phantom with differing oxygen conc., (B) transverse image of spin density and (C) the corresponding line width image from the procedure of Fig.2. (D) the linearity of the line width from T_2* vs. pO_2.

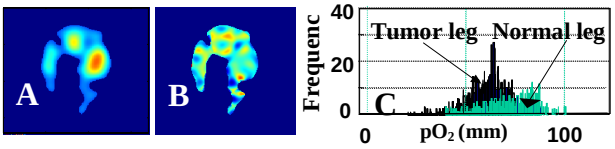

Fig. 3 Single Point 2D image (A) of a C3H mouse with its normal (left) and tumor (SCC) legs inside a 25mm x 25 mm resonator. 2D images taken with gradients ramped in 11 x 11 steps with a maximum gradient of 0.7 G/cm. SPI oxymetry was performed by considering 32 delay values of τ ranging from 700 ns to 1072 ns in 12 ns steps. The image matrix was 128 x 128 in size with a field of view of 40 x 40 mm at τ = 1072 ns. Processing of the data (Fig.1) leads to (A)spin density image, (B) pO_2 image and (C) pO_2 histograms in the normal and tumor leg shown on the right .

References: [1] Emid S and Creyghton JHN. *Physica* **B;128**:81-83 (1985). [2] S. Subramanian et al. *J. Magn Reson*;**137** 379-388 (1999).[3] S. Subramanian et al. *Magn. Reson. Med.* **48**: 370-379 (2002)