Dartmouth GEISEL SCHOOL OF MEDICINE

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Quantitative MRI Oximetry: Combining EPR and OE-MRI for Volumetric Mapping of Hypoxia in Tumors

COMING TOGETHER TO FORGE AHEAD IN MEDICAL PHYSICS

DARTMOUTH ENGINEERING

Abstract

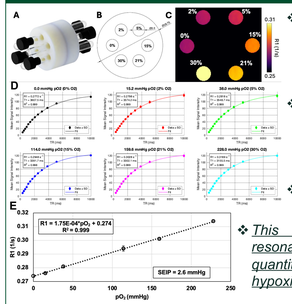
Purpose: Tumor hypoxia—a state of reduced oxygen supply—is well known to affect treatment response, particularly in radiotherapy and chemotherapy. Oxygen-enhanced magnetic resonance imaging (OE-MRI) uses oxygen's paramagnetic properties to map tissue oxygenation, where increased oxygen raises the spin-lattice relaxation rate R1. Modulating inhaled oxygen levels enables the identification of tumor regions with varying oxygenation. This study applies OE-MRI on a 9.4T MRI system to exploit high SNR and spatial resolution for oxygen mapping and to validate the R1-pO_2 relationship.

Methods: In-vitro and in-vivo experiments confirmed the expected R1-pO_2 linear relationship. An in-vitro study comparing R1 values with EPR[1] pO_2 data verified the expected calibration curve, confirming OE-MRI's accuracy and reproducibility. An OE-MRI evaluation of a murine brain alternated breathing gases (21% and 100% O_2) and simulated severe hypoxia with post-euthanasia imaging. R1 maps using saturation-recovery confirmed OE-MRI's sensitivity to oxygen changes in brain tissue. A tumor study utilized OxyChips[2] implanted in an SCC7 tumor on a C3H mouse. Micro-CT verified chip positions. R1 mapping and EPR oximetry measured pO_2 while inhaling 21% and 100% O_2 to generate a tissue-specific calibration curve for quantitative pO_2 mapping.

Results: R1 values correlated with EPR pO_2 measurements agreed well with previous experiments in the relaxivity range (1.42–2.08 $x10^{-4}$ 1/s/mmHg)[3]. The murine brain evaluation demonstrated OE-MRI's oxygen sensitivity at high field strength. *Tumor studies generated a tissue-specific calibration curve that linked R1 to pO2, enabling high-resolution, quantified mapping of hypoxia.*

Conclusion: OE-MRI calibrated with EPR oximetry can generate useful maps of hypoxia. These results support its potential applicability in adaptive radiation therapy and precision oncology. Future work includes refining calibration, reducing the size of the OxyChip, and exploring these techniques using low-field MR-LINAC systems.

Introduction



- In an external magnetic field, oxygen distorts the local magnetic field of nearby tissue, acting as a contrast agent to enhance regions of higher oxygen concentration.
- Oxygen-enhanced MRI (OE-MRI) leverages diatomic oxygen's (O_2) paramagnetic properties to provide a quantitative measure of the change in the surrounding tissue's spin-lattice relaxation rate (R1).
- This information can be utilized to generate comparative maps of tissue oxygenation.
- *This study combines electron paramagnetic resonance (EPR) oximetry, which offers absolute quantitative oxygen data, with OE-MRI to generate hypoxia maps inside tumors.*

Fig. 1 (above): OE-MRI of aqueous phantoms with varying oxygen concentrations. (A) Rendering of phantom. (B) Diagram of phantom. (C) R1 mapping using T1-saturation. (D) Saturation recovery fit for each vial. (E) Slope of R1 vs. pO_2 calibration curve (***1.75 $x10^{-4}$ 1/s/mmHg, r = 0.9995, p<0.001***) matches the expected range (1.42–2.08 $x10^{-4}$ 1/s/mmHg) based on empirical models.

Methods and Materials

- OEMRI was validated in a murine study prior to conducting the main experiment, which aimed to validate the MRI system's capacity to detect changes in tissue oxygen concentration.
- The experiment was performed at 9.4T using a 20 mm Bruker surface coil. R1 maps were computed voxel-by-voxel using RARE variable repetition time saturation-recovery relaxometry.
- The mouse was imaged while breathing 21% O_2, 100% O_2, and then ~30 minutes after expiring.

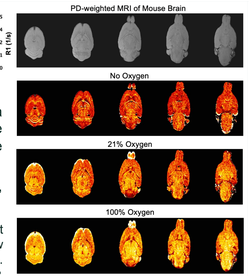
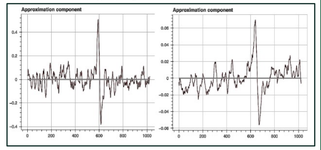
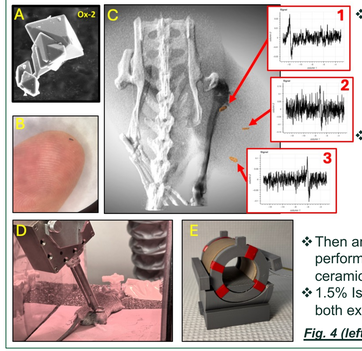


Fig. 2 (right): R1 maps of murine brain for different breathing conditions (not in chronological order). (A) PDw image. (B) Recently deceased. (C) 21% O_2. (D) 100% O_2.

- EPR oximetry uses spectroscopy to measure pO_2 using the horizontal peak-to-peak distance (linewidth), which is measured in Gauss and linearly proportional to pO_2. ***As pO_2 increases, so does the linewidth*** (**Fig. 3**).
- FDA-approved OxyChips[2] use LiNc-BuO (**Fig. 4A**), an EPR spin probe, to measure pO_2 in tissue quantitatively.

Fig. 3 (below): Noise-reduced spectrum of the 2nd chip (**Fig 4C.2**) used to measure linewidth at 21% (left) & 100% (right) O_2. De-noised using NERD[4].





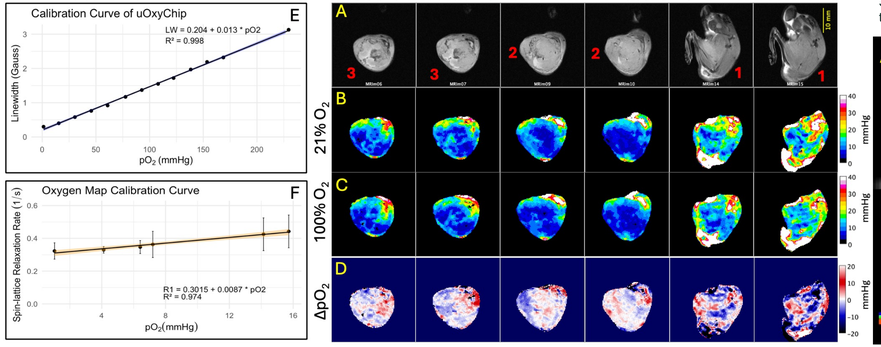
- 3 micro-OxyChips (**Fig. 4B**) coated with gold nanoparticles (GNPs) were implanted into an SCC7 tumor in the right flank of a mouse. GNPs allow for easier detection in μCT (**Fig. 4C**) and MRI.
- L-band EPR (**Fig. 4C.1-3, and 4D**) for each micro-OxyChip (No. 1-3) at two different oxygen conditions (21% and 100% O_2) gives 6 EPR measurements (3 chips x 2).
- Then an OE-MRI experiment was performed using a novel custom-built ceramic RF volume coil (**Fig. 4E**) at 9.4T.
- 1.5% Isoflurane was used throughout both experiments.

Fig. 4 (left): Experimental overview.

Results

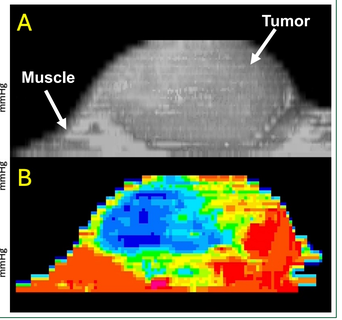
- T1- and T2-weighted anatomical scans help to identify the tumor boundary for reference and locate the three micro-OxyChips.
- The OxyChips provide no MR signal, but the GNPs create a slight "halo" around the chips, making them easy to spot.
- After the R1 maps were generated, ROIs of tissue near the micro-OxyChips were sampled to determine the average R1 value in the vicinity of the chips. These were plotted against the pO_2 detected using EPR to make a calibration curve of R1 vs. pO_2.
- This generated pO2 maps of the tumor and surrounding tissue. Resolution: 234μm x 234μm x 600μm.

Fig. 5 (below): MRI Oximetry with calibration curves. (A) T1-weighted anatomical scan of the tumor. From left to right, the slices move from the outer edge of the tumor to the leg muscle. Red numbers indicate which micro-OxyChips are visible. (B) pO_2 map of the tissue while breathing normal air. (C) pO_2 map of the tissue while breathing 100% O_2. (D) ΔpO_2 map. (E) OxyChip calibration curve. (F) pO_2 map calibration curve.



- The SCC7 tumor was shown to be highly hypoxic (*<10mmHg*) and possibly necrotic throughout most of the volume. The tumor showed only a minor increase in tissue oxygenation when breathing 100% O_2 with a very heterogeneous response.

Fig. 6 (below): (A) A top-view 3D T1-weighted MRI projection of the tumor and leg tissue. (B) A top-view 3D oxygen map (projected) of the tumor and boundary tissue. Blue = hypoxic tissue; Red is well-oxygenated.



Discussion

- The successful integration of discrete EPR calibration points with high-resolution MRI relaxometry demonstrates a novel solution to OE-MRI's fundamental limitation of providing only relative oxygen changes.
- This protocol enables absolute pO_2 quantification while maintaining high spatial resolution and the minimally invasive nature essential for clinical implementation.
- The observed heterogeneous hypoxic distribution within SCC7 tumors, with severely hypoxic cores (<10 mmHg) transitioning to more oxygenated peripheries, validates known tumor biology.
- The demonstrated capability for 3D hypoxia mapping positions this technology for integration with MR-LINAC systems, potentially enabling simultaneous hypoxia assessment and adaptive radiation therapy delivery. This approach has the potential to reduce normal tissue toxicity while improving tumor control through precision dose painting based on oxygen status.

Conclusions / Future Directions

- Using discrete calibration points, a linear calibration curve can be generated and applied to R1 maps to compute high-resolution 3D hypoxia maps of tumor sub-volumes.
- These results verified the expected outcome that most of the sub-volume of these tumor types is hypoxic, while some heterogeneity exists throughout the tumor tissue. One can also see that the tumor becomes more oxygenated near the periphery as the tissue approaches muscle tissue.

- Ultimately, this project aims to utilize 3D pO_2 mapping for hypoxia-targeted radiation-boosted treatment, thereby reducing the overall patient dose while increasing the tumor control probability.
- Transfer these techniques from ultra-high-field MRI to the low-field MR-LINAC environment, for simultaneous 3D hypoxia mapping and targeted radiation treatment.

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