Overhauser Oxygenation Imaging: Physics, Instrumentation and Pre-Clinical Applications

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Motivation: What needs to be measured?

Motivation: On what magnitude scale?

Table 1: Critical $O_2$ tensions below which typical cellular functions in solid tumors progressively cease or anticancer treatments are impaired as a result of an inadequate $O_2$ availability.

<table>
<thead>
<tr>
<th>Critical $O_2$ tension ($\mu$mol/l)</th>
<th>Function or parameter observed</th>
<th>Selective reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-35</td>
<td>Effectiveness of certain (passive) immunotherapies</td>
<td>(128)</td>
</tr>
<tr>
<td>15-35</td>
<td>Cell death with photodynamic therapy</td>
<td>(129-132)</td>
</tr>
<tr>
<td>25-30</td>
<td>Cell death on exposure to $\alpha$- and $\gamma$-radiation</td>
<td>(123)</td>
</tr>
<tr>
<td>10-20</td>
<td>Binding of hypoxia markers</td>
<td>(87, 95)</td>
</tr>
<tr>
<td>1-155</td>
<td>Proteasome changes</td>
<td>(22, 119-121, 125, 129)</td>
</tr>
<tr>
<td>0.2-1</td>
<td>Genome changes</td>
<td>(19, 22, 22, 29)</td>
</tr>
</tbody>
</table>

*nmol/l = millimolar of oxygen.

Continuous oxygenation mapping preferable.

Motivation: On what timescale?

Fluctuations in $pO_2$ in poorly and well-oxygenated spontaneous cancer tumors before and during fractionated radiation therapy

K.O. Bruck et al. / Radiotherapy and Oncology 77 (2005) 120-126

Significant fluctuations on a timescale of minutes exist.
Electron Paramagnetic Resonance Imaging (EPRI)

- Inject a free radical (unpaired electron) spin probe
- Use magnetic resonance to map spin probe properties and temporal dynamics

- Trityl, oxygen-sensitive line broadening. Image broadening.
- Nitroxide, redox potential similar to tissue. Image temporal decay.

With proper probes EPR sensitive to redox and oxygenation

NMR vs. EPR

- Nuclear spins
  - $T_1, T_2 \sim 1 \text{ s}$
  - $\gamma_e \approx 660$

- Electron spins
  - $T_{1e}, T_{2e} \sim 1 \mu\text{s}$

For the same B0, electrons have more polarization, higher resonance frequency, shorter $T_1, T_2$.

"Overhauser proposed ideas of startling originality, so unusual that they initially took portions of the scientific community back, but of such depth and significance that they opened vast new areas of science."

- Dynamic nuclear polarization, DNP
- Proton Electron Double Resonance, PEDRI
Nuclear-electron spin interaction

\[ H = -\hbar \gamma \mathbf{I} \mathbf{B}_{ext} \mathbf{I} - \hbar \gamma \mathbf{S} \mathbf{B}_{ext} \mathbf{S} + \hbar H' \]

\[ H' = -\left(\frac{\hbar \gamma \mathbf{I} \mathbf{S}}{r^2}\right) \left[\frac{3(1 \cdot \hat{r}) (\mathbf{S} \cdot \hat{r})}{r^2} - \mathbf{I} \cdot \mathbf{S}\right] \]

\[ \mathbf{I} = \frac{\mathbf{I}}{\gamma_I}, \quad \mathbf{S} = \frac{\mathbf{S}}{\gamma_S} \]

Net nuclear magnetization
\[ \langle I_z \rangle = (N_{\uparrow\uparrow} + N_{\uparrow\downarrow}) - (N_{\downarrow\uparrow} + N_{\downarrow\downarrow}) \]

Net electron magnetization
\[ \langle S_z \rangle = (N_{\uparrow\uparrow} + N_{\downarrow\downarrow}) - (N_{\uparrow\downarrow} + N_{\downarrow\uparrow}) \]

No saturation case

\[ \langle I_z \rangle = I_0 \]

\[ \langle S_z \rangle = S_0 \]

Leakage factor
\[ f = \frac{w_{t} + 2w_{s} + w_{r}}{(w_{t} + 2w_{s} + w_{r})} \frac{\tau c}{1 + \tau c} = rcT \]

Saturation factor
\[ s = \frac{\langle S_z \rangle - S_0}{S_0} = \frac{\gamma S B_{ext} T_{1e} T_{2e}}{1 + \gamma S B_{ext} T_{1e} T_{2e}} \]

Saturation factor
\[ s = \frac{\langle S_z \rangle - S_0}{S_0} = \frac{\gamma S B_{ext} T_{1e} T_{2e}}{1 + \gamma S B_{ext} T_{1e} T_{2e}} \]
Complete saturation

nuclear spins

\[ < I_z > = \left( 1 - k_f \gamma_s \gamma_I \right) I_0 \sim -300 I_0 \]

< S_z >= 0

saturating RF

electron spins

Heisenberg Spin Exchange Interaction

\[ \Delta \omega_{ex} = 4\pi R \times D_{ij} \times \left( D_{ij} + D_{ji} \right) \]

Exchange broadening equals diffusion collision frequency \( \omega \) (Salikhov, Smoluchowski)

Oxygen effect

\[ \frac{1}{T_2} \propto C_{O_2} \]

\[ \text{FIG. 10. The oxygen effect on } T_2 \text{ for deuterated hydroyxy tertyl in water at } 37^\circ C \]


Heisenberg Spin Exchange

\[ \Delta \omega_{ex} = 2\pi R \times D_{ij} \times [SP] \]

\[ \text{FIG. 7. The peak-peak linewidth and } \Delta \text{ the Lorentzian linewidth, } 2\pi R \times D_{ij} \text{ for the deuterated hydroyxy tertyl in isotonic saline for the deuterated hydroyxy tertyl at } 37^\circ C \]

Overhauser enhancement summary

\[ I_x - I_0 = \left( \frac{\gamma_x}{\gamma_0} \right) f \kappa \]

\[ f = \tau c T_1 \text{ (leakage factor) } \]

\[ \kappa = 0.5 \text{ (coupling factor, purely dipolar interaction) } \]

\[ x = \left\{ \begin{array}{c} \frac{\gamma_x B_0 T_1 T_2}{1 + \gamma_x B_0 T_1 T_2} - \frac{\alpha \gamma_x B_0 T_1 T_2}{1 + \gamma_x B_0 T_1 T_2} \text{ (saturation factor) } \\
\end{array} \right. \]

\[ \left\{ \frac{\gamma_x B_0 T_1 T_2}{1 + \gamma_x B_0 T_1 T_2} \right\}^2 = a_i c_{i+1} + a_{-i} c + a_i \]

Overhauser Enhancement reports spin probe parameters via its dependence on spin probe concentration and relaxation times. It also depends on EPR rf power \((B_0)\), EPR pulse duration.

Instrumentation


Overhauser enhanced magnetic resonance imaging for tumor oximetry

TR / T_EPR: 1000 ms / 400 ms

64x64, 0.5 mm x 0.5 mm x 5 – 10 mm

Spin-echo OMRI acquired using two RF power levels for phantoms with various trityl concentrations and oxygenations.

<table>
<thead>
<tr>
<th>Trial concentration</th>
<th>High power (22 W)</th>
<th>Low power (0.3 W)</th>
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<tbody>
<tr>
<td>1 mM</td>
<td>120 ± 20</td>
<td>98 ± 14</td>
</tr>
<tr>
<td>2 mM</td>
<td>190 ± 30</td>
<td>148 ± 16</td>
</tr>
<tr>
<td>3 mM</td>
<td>150 ± 22</td>
<td>114 ± 14</td>
</tr>
</tbody>
</table>


Simultaneous imaging of tissue pO2 and Ktrans of OX63 in vivo using Overhauser-enhanced MRL.

Five phantoms contained 3CP nitroxide. Various amounts of ascorbic acid were added as shown in the left diagram. Phantoms with additional 1-mM trityl are gray shaded.

Red, blue, and black denote 0, 5, 10 mM AsA addition. Solid circles, open circles, and cross marks represent trityl signal, 3CP signals with and without 1-mM trityl, respectively.
Applications

PMRI (May 25) demonstrates anatomic information with 5 mm tumor of bright T2 contrast. Fiducial tubing (1.6 mm i.d. filled with water) is visible between the two legs. The mouse underwent pO2 and redox OMRI 3 days later. Trityl and 3CP were consecutively infused by intratumoral injection.


Determination of position of LiPc implantation on an image of HM-PROXYL probe.

Summary

- Dynamic nuclear polarization (Overhauser) offers possibility for quantitative imaging of oxygenation and redox status in pre-clinical models
- RF power deposition main obstacle to clinical translation
- Offers potential for correlative studies with number of simultaneously monitored parameters and anatomi cal context
Thank you