How to perform BOLD-MRI in body tumours: feasibility study

Poster No.: C-2435  
Congress: ECR 2015  
Type: Scientific Exhibit  
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Keywords: Oncology, MR physics, Molecular imaging, MR-Functional imaging, Chemotherapy, Radiation therapy / Oncology, Metastases, Neoplasia  
DOI: 10.1594/ecr2015/C-2435

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Aims and objectives

AIMS

1. Describe the physical basis and how to perform Blood Oxygen Level Dependent (BOLD) MRI with hyperoxia in the body
2. Highlight how BOLD-MRI can be performed for the analysis of tissue oxygenation and angiogenesis of different body tumors

Background

Tumor hypoxia is one of the main cancer hallmarks, as it promotes cell division, invasion, angiogenesis and metastatic risk. Interestingly, it has been related to increase resistance to several treatment types as radiation, chemotherapy, thermal ablation and photodynamic therapies. Different efforts have been spent in order to measure tissue oxygenation of cancer, as it predicts the radiation response and regional tumor control.

Different approaches with PET and MRI have been tested for noninvasive quantification of oxygenation. Dynamic contrast enhanced MRI (DCE-MRI) has shown to provide indirect estimates of hypoxia but with not clear relationship to tumor hypoxia. Interestingly, BOLD-imaging has demonstrated interesting results in the evaluation of tissue hypoxia with different approaches.

Changes in concentration of paramagnetic molecules (e.g.: deoxyhemoglobin) in and around vessels create local variations in the image phase, which are identified as a decay of signal on T2* sequences. The concentration of deoxyhemoglobin within the vessel increases with rising oxygen consumption, leading to a decreasing T2* relaxation time of surrounding tissue. The rate of spin dephasing (R2*=1/T2*) is an index of the oxygenation of tissue.

Native relaxometry with BOLD (calculation of native tissue R2*) is easy to perform but show clear limitations in specificity. Most commonly, T2* measurements have been performed, as short values of the reversible transverse relaxation time T2* are related to low blood oxygenation, due to the paramagnetic nature of deoxygenated blood. In the body, this approach has been used to demonstrate differences in R2* between solid and cystic renal lesions. However, T2* is not only related to blood oxygen saturation but also...
to tissue T2, local magnetic field variations, hematocrit level, and vessel microstructure. Therefore, if the blood flow is high and the hemoglobin saturation rate is low, then R2* only reflects the blood flow of the studied tissue.

More promising are BOLD approaches using physiologic and pharmacologic challenges such as hyperoxia (inhalation of oxygen at high concentrations), hypoxia (breath-holding) or hypercapnia (inhalation of Carbogen: 95% O2/5% CO2). Relative changes in R2* (#R2*) in response to these challenges are a better biomarker of pO2 than the absolute value of R2*. An increase of R2* in an area of tissue compared to other part of the same organ under the same pathological circumstances, has been related to the existence of hypoxia.

Oxygen-enhanced R2* measurements is a promising technique to interrogate tumor oxygen delivery and hypoxia, although little clinical experience with this technique has been accumulated by the moment. It requires of the delivery of oxygen-enriched air to patients, and provides a qualitative assessment of tumor hypoxia, although does not require any dedicated hardware of postprocessing software. This approach measures #R2*- and R2-weighted signal intensities in response to oxygen breathing scales compared with baseline [deoxyhemoglobin: deoxyHb]. BOLD measurements with hyperoxia have shown a good correlation with tissue changes in pO2, as it measures the hypoxia secondary to the fall of perfusion or the acute hypoxia secondary to the functional and structural abnormalities of tumor neoangiogenesis. Reported limitations of this technique are limited specificity for high sO2, low blood volume or in cases of oxygen-steal. In addition, the underlying hemodynamic and oxygenation-related mechanisms are far from being fully understood. However, it lacks of potential complications as the use of carbogen, which may cause respiratory distress.

DCE-MRI may provide an indirect estimation of tumor hypoxia, as it gives information of the total vascular volume of the tumor; whereas BOLD MRI is sensitive only to vessels where gaseous interchange occurs. It is well known that in tumors, not all neovessels show effective blood cell transport due to vascular occlusions. Therefore, hypoxic tumors with high blood volume will show a greater #R2* to physiological challenges, and are theoretically candidates for radiosensitisation. In the body, preliminary data has shown promising results for cervical and prostate cancers. However, BOLD-MRI is still in the preclinical phase due to lack of standardization of technique, multiple approaches and different outcomes chosen for comparison.

**Basis of BOLD imaging**
BOLD imaging is based on the effect that paramagnetic molecules of the blood (e.g.: deoxyHb) produce on local fields. They create local variations in the image phase, which are identified as a variation (decay) of signal on T2* sequences.

If pure O$_2$ is administered, there is an increase pass of O$_2$ from blood to the tissue. The concentration of deoxyHb increases with rising oxygen consumption, leading to a decreasing T2* relaxation time of the surrounding tissue (Fig. 1 on page 5). The connection between changes in BOLD sequences and tissue oxygenation can be explained through the relationship between oxygen and Hb in the blood. DeoxyHb has an iron atom that directly influences the magnetic fields producing a local signal drop.

BOLD imaging measures the hypoxia secondary to the fall of perfusion or the acute hypoxia secondary to the functional and structural abnormalities of tumor neoangiogenesis. The rate of spin dephasing, R2*, is an index of the oxygenation of tissue (1/T2*). If the blood flow is high and the Hb saturation rate is low, then R2* only reflects the blood flow of the studied tissue. An increase of R2* (drop of T2* and positive #R2*) in an area of tissue compared to other part of the same organ under the same pathological circumstances, is due to the existence of hypoxia.
Fig. 1: If pure O2 is administered, there is an increase pass of O2 from blood to the tissue. The concentration of deoxyHb increases with rising oxygen consumption, leading to a decreasing T2* relaxation time of the surrounding tissue.

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Methods and materials

BOLD-MRI with hyperoxia was performed in 14 patients with confirmed body malignancies (Table 1) and submitted to MRI for locoregional and/or distant staging. Our institutional review board approved our study and informed consent was obtained from all patients.

Table 1. Study population

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate adenocarcinoma</td>
<td>1</td>
<td>62</td>
<td>Male</td>
</tr>
<tr>
<td>Rectal adenocarcinoma</td>
<td>2</td>
<td>48/69</td>
<td>Male/Female</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>1</td>
<td>50</td>
<td>Female</td>
</tr>
<tr>
<td>Cervical uterine carcinoma</td>
<td>1</td>
<td>53</td>
<td>Female</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>1</td>
<td>47</td>
<td>Female</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>1</td>
<td>69</td>
<td>Female</td>
</tr>
<tr>
<td>Retroperitoneal liposarcoma</td>
<td>1</td>
<td>69</td>
<td>Male</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>1</td>
<td>83</td>
<td>Male</td>
</tr>
<tr>
<td>Clear cell Renal carcinoma (RCC)</td>
<td>1</td>
<td>54</td>
<td>Male</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1</td>
<td>62</td>
<td>Male</td>
</tr>
<tr>
<td>Liver metastasis (neuroendocrine tumor)</td>
<td>1</td>
<td>52</td>
<td>Male</td>
</tr>
<tr>
<td>Liver metastasis (colorectal carcinoma)</td>
<td>1</td>
<td>50</td>
<td>Male</td>
</tr>
</tbody>
</table>
Non Small Cell Lung cancer (NSCLC) | 1 | 50 | Male

**MRI study**

All studies were performed in a 3T magnet (Achieva. Philips. Best. Netherlands) using a phased-array body coil of 16 elements.

BOLD-MRI was included as part of the MRI protocol for staging. MRI protocols varied accordingly to tumor type and location

**BOLD MRI**

Fig. 2 on page 9 represents the 3 steps of our BOLD acquisition:

**Step 1. Acquisition of multiecho Fast Field Sequence**

A multiecho FFE T2* sequence (Fig. 3 on page 10) was performed.

Two different of acquisitions strategies were used, each of one in 7 patients. Protocol 1 included a multiecho FFE acquisitions in basal conditions and 5, 10 and 15 minutes after the inhalation of pure O₂ (5 l/mn).

Protocol 2 included multiecho FFE acquisitions in basal conditions and 2, 5, 7 and 10 minutes after the inhalation of pure O₂ (5 l/mn). A final acquisition 3 minutes after cessation of O₂ administration was also performed.

**Table 2. Patients submitted to different BOLD-MRI protocols**

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate adenocarcinoma</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>Rectal adenocarcinoma (2)</td>
<td>Cervical uterine carcinoma</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Ovarian carcinoma</td>
</tr>
<tr>
<td>Retroperitoneal liposarcoma</td>
<td>Pancreatic adenocarcinoma</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Renal cell carcinoma (RCC)</td>
</tr>
<tr>
<td>Non Small Cell Lung cancer (NSCLC)</td>
<td>Liver metastasis (neuroendocrine tumor)</td>
</tr>
<tr>
<td></td>
<td>Liver metastasis (colorectal carcinoma)</td>
</tr>
</tbody>
</table>
**BOLD sequence design:**

13 different echo od times from 2.3 to 30 ms

Echo spacing: 2.3 ms to avoid fat contamination on the T2* estunatuob

Flip angle relatively high (#{25}) to obtain T1-weighting in the first echo image and evalaute T1 changes due to oxygen variations

**Step 2. T2* estimation**

Signal intensity of all echoes were fitted to a mono-exponential decay model to estimate the T2* values of every pixel (Fig. 4 on page 13).

T2* was estimated for each acquisition and R2* was also calculated.

**Step 3. Fusion of T2* mapping and anatomical image and #R2* curves**

T2* maps of each acquisition were fused with TSE T2-weighted image in order to obtain a fusion image, that permitted a visual evaluation of the changes produced in the tumor with the hyperoxia (Fig. 5 on page 11). Fig. 6 on page 12 explains how these maps can be read. In addition, a ROI in the solid component of the tumor was drawn in the original T2* map, and then the ROI was copied and pasted in the rest of acquisitions, in order to monitoring #R2* during the different acquisitions using a graphic representation (Fig. 7 on page 9).

Hypoxic tumors with high blood volume show greater #R2* to oxygen challenge. Therefore, an ascending or flat curve of #R2* during O₂ administration was considered as a sign of radioresistance and a descending curve of #R2* related to radiosensitivity.
Fig. 2: Diagram shows the three steps of each BOLD acquisition: 1. Performance of a multiecho Fast Field Sequence with 13 different echo times from 2.3 to 30 ms. Echo spacing 2.3 ms to avoid fat contamination on the T2* estimation. Flip Angle relatively high (a=25) to obtain T1 weighting in the first echo image and evaluate T1 changes due to oxygen variations. 2. T2* estimation: signal intensity of all echoes are fitted to a mono-exponential decay model to estimate the T2* values of every pixel. 3. Fusion on T2 TSE sequence and T2* mapping to obtain a color parametric map

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Fig. 7: Diagram represents the different time of acquisitions of our BOLD approach with hyperoxia: basal acquisition, acquisition after 95% O2 breathing at 5, 7 and 10 mn and finally an acquisition without O2

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BOLD MRI

- mFFE sequence for $T_2^*$ mapping
- Different echo signals are acquired with the same excitation pulse
- We perform a dynamic acquisition before and after hyperoxia (95% $O_2$ inhalation)

Fig. 3

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Fig. 5

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Fig. 6

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Signal intensity of all echoes were fitted to a monoexponential decay model to estimate the T2* values of every pixel.

**Fig. 4**

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Results

All studies were perfectly tolerated and could be performed satisfactorily. There was no complications during any of the procedures.

11 malignancies (78.6%) showed a descending curve during the first 5 to 7 mn of O₂ administration (Fig. 8 on page 17 and Fig. 9 on page 17) related to radiosensitivity.

2 tumors (14.2%) demonstrated an ascending curve during the first 5 to 7 mn of O₂ administration (Fig. 10 on page 18 and Fig. 11 on page 19).

1 cancer (7.2%) showed a flat curve (Fig. 12 on page 20).

Ascending and flat curves were related to radiosensistance.

In the comparison between the 2 different groups of protocols. In 5 of 7 cases (71.4%) using protocol 1, an increase in #R₂* after 5 to 10 mn of O₂ administration (Fig. 8 on page 17) was demonstrated, probably due to saturation of gaseous interchange between vessel and tumor. This delay ascent was detected in 5 of 6 cases (83.3%) showing a descendent curve, except in the case of prostate adenocarcinoma (Fig. 9 on page 17).

In all the tumors submitted to protocol 2, between 5 to 10 minutes after O₂ administration the curve of #R₂* changed its morphology to return in the delayed acquisition without O₂ to similar levels of oxygenation that in basal conditions. This effect was appreciated either in cases showing an ascendent curve (Fig. 10 on page 18), or a descendent one (Fig. 13 on page 21). This is, the initial and final oxygenation during BOLD imaging of all tumors submitted to protocols 2 were very similar.

Table 3. Curve type in tumors submitted to protocol 1

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Curve type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate adenocarcinoma</td>
<td>Descendent</td>
</tr>
<tr>
<td>Rectal adenocarcinoma (2)</td>
<td>Descendent (2)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Descendent</td>
</tr>
<tr>
<td>Retroperitoneal liposarcoma</td>
<td>Flat</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Descendent</td>
</tr>
<tr>
<td>Non Small Cell Lung cancer (NSCLC)</td>
<td>Descendent</td>
</tr>
</tbody>
</table>
Table 4. Curve type in tumors submitted to protocol 2

<table>
<thead>
<tr>
<th>Protocol 2</th>
<th>Curve type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial carcinoma</td>
<td>Descendent</td>
</tr>
<tr>
<td>Cervical uterine carcinoma</td>
<td>Descendent</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>Descendent</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>Ascendent</td>
</tr>
<tr>
<td>Renal cell carcinoma (RCC)</td>
<td>Ascendent</td>
</tr>
<tr>
<td>Liver metastasis (neuroendocrine tumor)</td>
<td>Descendent</td>
</tr>
<tr>
<td>Liver metastasis (colorectal carcinoma)</td>
<td>Descendent</td>
</tr>
</tbody>
</table>
**Fig. 8:** HCC using protocol 1 shows an initial descent in R2* during the first 5 minutes of O2 administration and a delay ascent of R2*
Fig. 9: Prostate adenocarcinoma. BOLD imaging using protocol 1 demonstrated a descent in R2* signal during all point time of O2 administration

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Fig. 10: Pancreatic carcinoma submitted to protocol 2 which shows an ascendent curve of R2* during the first 5 minutes of O2 administration and delayed descent of R2*.

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**Fig. 11:** Clear cell renal carcinoma. BOLD imaging was obtained using protocol 2. This tumor showed increase values of R2* during of O2 administration with a decrease in R2* after O2 cessation.

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**Fig. 12:** Retroperitoneal liposarcoma which shows a small peripheral solid nodule (arrow) submitted to BOLD imaging using protocol 1 and demonstrating a flat curve (absence of gaseous interchange in solid component)

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**Fig. 13:** Ovarian serous cystadenocarcinoma submitted to BOLD imaging using protocol 2 demonstrates a descent curve during the first 5 minutes after O2 administration with a delay ascent of R2* values in the rest of acquisitions.

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Conclusion

- BOLD-MRI with hyperoxia is feasible in different body regions in a clinical setting, allowing the assessment of tumor neoangiogenesis and hypoxia.
- According to this short series, BOLD-MRI with hyperoxia at 3T has the potential to estimate tumor hypoxia which may be of interest for treatment selection and therapy monitoring.
- This preliminary data suggests that BOLD-MRI with hyperoxia can be performed as part of the MRI assessment of body malignancies in different organs and systems.
- After 5 to 10 minutes of $O_2$ administration a saturation effect in gaseous interchange occurs, which can be better estimated with a protocol that limits $O_2$ administration to 10 mn and a final acquisition without $O_2$.
- Further research is needed to validate these short series and to further establish the clinical usefulness of this technique.
References