Complex relationship between changes in oxygenation status and changes in R2* : the case of insulin and NS-398, two inhibitors of oxygen consumption.

B. F. Jordan[1], N. Crokart[1], C. Baudelet[1], G. O. Cron[1], R. Ansiaux[1], B. Gallez[1]

[1]Biomedical magnetic resonance unit, Université Catholique de Louvain, Brussels, B, Belgium

Introduction:

Insulin and NS-398 have been reported to inhibit oxygen consumption in experimental tumor models, thereby increasing oxygenation and radiosensitization (1,2). The aim of this work was to use MRI to study changes in murine FSaII tumor hemodynamics after administration of those oxygen consumption inhibitors. We compared BOLD parameters with DCE-MRI data as well as with pO_2 results obtained by EPR oximetry.

Materials and Methods:

A multiple-echo gradient-echo MRI sequence (4.7 T) was used to map changes in the following three quantities: the BOLD signal (at TE=20 ms), the parameter S0 (theoretical signal at TE=0 ms), and the relaxation rate R2*. DCE-MRI provided perfusion derived parameters: vp, Ktrans, number of perfused voxels. EPR oximetry was used to monitor tumor pO2 over time.

Results:

Insulin caused a significant decrease in tumor BOLD signal over time (Figure 1). This was likely the result of decreased blood flow, since both S0 and the percentage of perfused tumor decreased as well (DCE-MRI indicated that less tumor regions are perfused after insulin: 56.3±7.2% for insulin vs 71.2±4.5% for control, $p<0.05$).Tumor R2* did not change significantly in response to the treatments, which is surprising considering that other non-MRI techniques (EPR oximetry, fiber optic probes) have shown that tumor oxygenation increases after treatment (Figure 2). Similar results were obtained using NS-398 (data not shown).

Discussion:

It was interesting to use insulin and NS-398 as they have a complex effect on tumor hemodynamics: they induced an increase in tumor oxygenation by an inhibitory effect on cell oxygen consumption, while they produced a decrease in tumor perfusion. Variations in BOLD SI and R2* did not reflect the change in pO2. To explain the discrepancy between changes in pO2 and the lack of change in R2*, it may be noted that EPR provides extracellular measurements whereas ΔR2* results from the intravascular compartment only. Moreover, metabolic changes associated with vasoactive challenges might have an unpredictable influence on blood saturation and R2*. In conclusion, this study further emphasizes the fact that changes in BOLD signal and R2* in tumors do not depend uniquely on changes in oxygenation status.

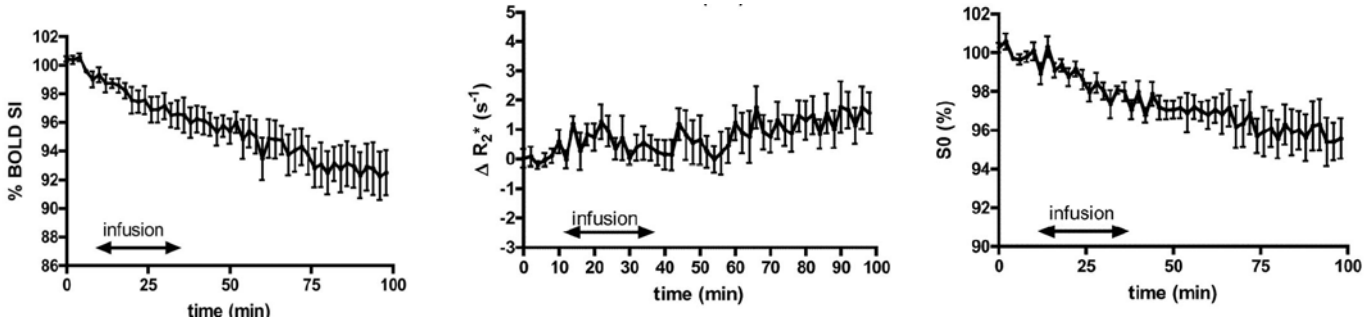

Figure 1:

Effect of insulin (infusion) treatment on the hemodynamic parameters using a multiple-echo gradient-echo sequence on FSaII tumor bearing mice (n=6). Time evolution of the following three quantities: the BOLD signal (left), the change in relaxation rate R2* (middle), and the parameter S0 (theoretical signal at TE=0 ms, right). Note that the BOLD SI and S0 decreased with the time while the R2* was stable.

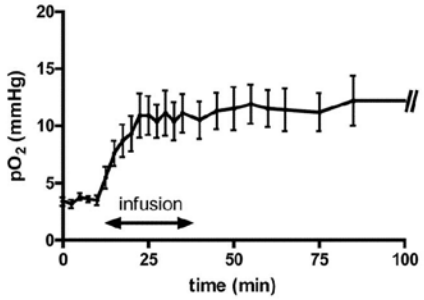

Figure 2 :

Effect of Insulin on the evolution of pO2 as a function of time measured by EPR oximetry on FSaII tumor bearing mice (n=5). Note also that the R2* does not correlate with the evolution of the pO2.

Références :

(1) Jordan BF, Gregoire V, Demeure RJ, Sonveaux P, Feron O, O'Hara J, Vanhulle VP, Delzenne N, Gallez B. Insulin increases the sensitivity of tumors to irradiation: involvement of an increase in tumor oxygenation mediated by a nitric oxide-dependent decrease of the tumor cells oxygen consumption. Cancer Res. 2002; 62: 3555-3561.

(2) Crokart N, Radermacher K, Jordan BF, Baudelet C, Cron GO, Grégoire V, Beghein N, Bouzin C, Feron O, Gallez B. Tumor radiosensitization by anti-inflammatory drugs : evidence for a new mechanism involving the oxygen effect. Cancer Res. 2005; 65: 7911-7916.