

## R2\* response of brain tumors to hyperoxic and hypercapnic respiratory challenges at 3 Tesla

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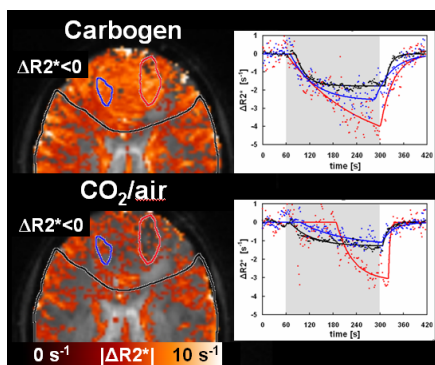
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**Introduction:** Changes in the MR relaxation rate R2\* directly correlate to those in the deoxyhemoglobin (dHb) concentration (BOLD effect) [1,2]. The modulation of the dHb concentration of venous blood by hyperoxic or hypercapnic respiratory challenges allows the assessment of tissue oxygenation and vasoreactivity. The knowledge of these parameters is of major diagnostic value in the field of oncology as it gives insight into a wide range of tumor parameters, e.g. the vascular growth, haemodynamic changes in the response to treatments, acute hypoxia, and vessel maturation [3,4]. Recently, we demonstrated that  $\Delta R2^*$  measurement is superior to balanced SSFP signal recording for the monitoring of respiratory challenges with carbogen and CO<sub>2</sub>/air in healthy volunteers [5]. Under both conditions the blood flow is increased [6] leading to decreased dHb concentrations (R2\*↓), which are of the same order as the oxygenation effects. However, the vasoreactivity of tumors might differ from that of healthy tissue. Now, we present first measurements of the  $\Delta R2^*$  response of cerebral tumors to these respiratory challenges.

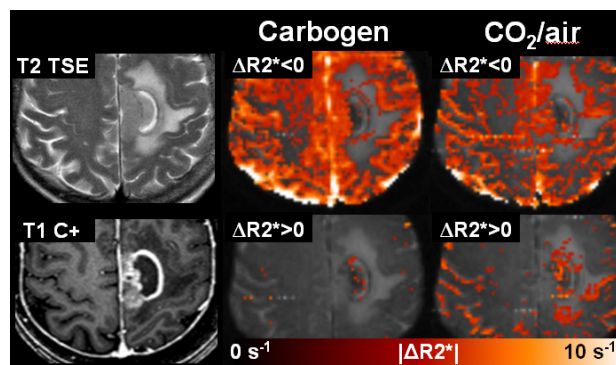
**Methods:** Five patients (aged 31 - 65 y) were included in the study (1 meningioma, 2 glioblastomas, 2 metastases). All MR imaging was performed on a 3 T clinical scanner (Achieva, Philips Medical Systems) using a transmit/receive head-coil to measure a transverse slice through the center of the tumor. The effects of respiratory challenges were monitored with a dynamic multi-gradient-echo sequence (acquisition time 7 min, 198 dynamics each with 12 echoes, TE/TR = 4-83/97 ms, flip angle 25°, echo-planar-imaging factor 5, voxel size 1.8×1.8×5 mm). The breathing protocol consisted of 1/4/2 min of breathing air/gas/air, respectively. Room air, carbogen (Cb: 95%O<sub>2</sub>/5%CO<sub>2</sub>) and the CO<sub>2</sub>/air gas mixture (5%CO<sub>2</sub>/25%O<sub>2</sub>/70%N<sub>2</sub>) were supplied through a facemask using a demand valve. The O<sub>2</sub> and CO<sub>2</sub> contents of the in- and exhaled gas mixture were continuously monitored to check tightness of the breathing system. All data processing and visualization was done offline using custom-built research software (Philips Research, Hamburg, Germany) realized as an IDL graphical user interface (IDL 6.3, RSI): After motion correction of the data, the dynamic change of R2\* was obtained from the ratio of the signal decays during respiratory challenge and baseline [7] to correct for large-scale susceptibilities. The  $\Delta R2^*$  time series were further analyzed voxel-wise for significant changes by comparing data of the respiratory challenge with baseline data during air breathing (student's t-test, p<0.001). Significant negative and positive changes were displayed as color-coded overlays over the peak height images in separate maps. The color scales with the absolute mean difference between the baseline and the response data which were used in the t-test.

**Results and Discussion:** Breathing of the gases was well tolerated by all patients. Different tumor areas, as identified by conventional MR imaging, showed different responses to the respiratory challenges. Meningioma: The entire tumor region showed a negative  $\Delta R2^*$  response (R2\*↓) to both gases. In a subarea, particularly large changes were induced by Cb breathing, which may reflect a high vessel density and/or a high oxygen consumption. Furthermore, the same area showed a delayed response to CO<sub>2</sub>/air in comparison to the healthy brain tissue, indicating a pathological altered vessel function (Fig. 1). Glioblastomas: Contrast enhancing tumor areas showed negative response (R2\*↓) to both gases, reflecting good venous vascularization and "normal" vasoreactivity. For necrotic areas and the perifocal edema, hardly any response was observed, however, a few subareas showed a positive response (R2\*↑) to CO<sub>2</sub>/air. This may be caused by vascular "steal" effect, which occurs during the vasodilation/increased cerebral blood flow of vessels in other tumor areas and may be indicative of pathological tumor vessels (Fig. 2). Metastases: Central parts showed negative response (R2\*↓) to both gases. The rim revealed positive response (R2\*↑) during CO<sub>2</sub>/air (Fig. 3) explainable by vascular "steal" effect.

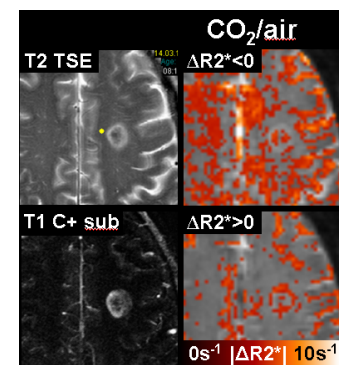
**Conclusion:** The proposed measurement of  $\Delta R2^*$  at 3 Tesla during respiratory challenges is sensitive enough to reflect the characteristically altered vessel function and reactivity in different tumor regions. In addition to the pure differentiation of pathologies, this may support the selection and dosage of therapies that require a certain degree of oxygenation or vascularization and it provides a tool for non-invasive contrast-agent-free monitoring of their outcome.



**Fig. 1:** Meningioma. Overlays of pixels with a negative response to Cb and CO<sub>2</sub>/air (left) and average response curves of the colored ROIs (right).



**Fig. 2:** Glioblastoma multiforme (WHO grade IV). T2-weighted and contrast enhanced T1-weighted images (left). Overlays of negative and positive responses to Cb (middle) and CO<sub>2</sub>/air (right).



**Fig. 3:** Metastasis. T2-weighted and contrast enhanced subtraction images (left). Overlays of the responses to CO<sub>2</sub>/air (right).

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