Novel MR method to detect non-normoxic tissue based on cluster analysis of the dynamic R2* and R, response to a hyperoxic respiratory challenge

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Introduction
Dynamic oxygen or carbon dioxide enhanced MRI is gaining increasing interest for the assessment of tissue oxygenation and vasoreactivity [1-7]. These are important parameters for the selection of cancer treatments, e.g. the efficiency of radiation therapies depends on the oxygenation level of tumors. Conventionally, these studies measure the response of the R2* or R relaxation rates to oxygen-enhanced respiratory challenges. The observed changes are expected to reflect the level of blood oxygenation (ΔR2*) and of dissolved oxygen in plasma and tissue (ΔR). Results are mostly presented as ΔR; or ΔR* response maps [1-7], by graphical representations of the dynamic ΔR, or ΔR* response over time [3,7], or by (ΔR*, ΔR) scatter plots [5,6], in which each voxel is represented with its multi-parametric response amplitude. Tumors show distinct values in the response maps, respond differently over time, and tumor voxels distribute differently in the (ΔR*, ΔR) scatter plots compared with normal tissue. Given the complexity of the information delivered by those experiments, there is a strong need for the comprehensive analysis of the ΔR, and ΔR* response functions allowing for the detection and depiction of abnormalities related to oxygenation. This work describes a novel approach of how to analyze and display the ΔR, and ΔR* response to an oxygen-enhanced respiratory challenge in order to differentiate normoxic from non-normoxic tissue.

Methods
The proposed method processes the voxel-wise response amplitude of ΔR1 and ΔR* to an oxygen enhanced respiratory challenge. The ΔR against ΔR* response amplitudes of all voxels are depicted in an (ΔR*, ΔR1) scatter plot (Fig 1c). A reference tissue region is defined manually including non-tumor voxels as confirmed by routine MR imaging (see green ROIs in Figure 1d and green crosses in Fig 1c). 5% of these voxels with the largest distance to their neighbors in the (ΔR*, ΔR1) scatter plot are assumed to be outliers and excluded from further analysis. The lowest ΔR* value and the lowest ΔR value of this reference cluster define the threshold for a voxel to be accepted as normal. The voxel with the lowest ΔR* value further determines the ΔR threshold. Voxels with an ΔR* and ΔR response lower than these thresholds (within the non-normoxic sections of Fig 1c) are classified as non-normoxic. These voxels are depicted in a color coded non-normoxic response map (Fig. 1d). Voxels in other parts of the plot and outside the reference cluster are assumed to be caused by either tissue with higher blood volume (*), high blood oxygen saturation (**), low blood volume and increased fluid content like edema (***), or vascular steal effects (****), according to the findings in [6]. These voxels are thus not included in the non-normoxic response map. 4 patients with intracranial tumors (1 metastasis, 2 glioblastoma, 1 lymphoma) were imaged on a 3T clinical scanner (Philips Achieva TX, The Netherlands) using a quadrature head coil. For simultaneous R1 and R* measurement, a dynamic RF-spoiled multi-gradient-echo steady-state sequence with a temporal resolution of 2.2s/frame and with REST slabs to minimize the influence of flow was used in combination with a baseline R1,0 and B2 measurement as previously described [6]. Data were registered and corrected for motion before ΔR* was estimated from the multi-echo decay and ΔR1 was estimated from the change of the extrapolated signal at TE=0. Imaging was carried out on a 3T clinical scanner (Philips Achieva TX, The Netherlands) using a quadrature head coil.

Results and Discussion
The most important findings were: 1) The majority of voxels was classified as normoxic. Only veins and tumor voxels enhanced in the non-normoxic response maps (see Fig 1d). Thus, the method seems to detect areas of low oxygenation, with the limitation that non-perfused hypoxic areas cannot be differentiated from areas where the confounding effects of a decreasing deoxyhemoglobin fraction and an increasing amount of paramagnetic oxygen molecules outbalance each other (zero-response). Experiments with different O2 or CO2 levels could further be used to increase specificity by separating the influence of vasoreactivity and residual flow changes. 2) The reference clusters and non-normoxic sections as defined above slightly differed among patients/anatomies. The use of a global reference cluster and global ΔR* and ΔR1 thresholds derived from larger patient or volunteer studies could further improve the robustness and accuracy of the approach. 3) In all cases, the algorithm detected voxels with a normal ΔR* but conspicuous ΔR; response amplitudes, and also voxels with conspicuous ΔR* but normal ΔR; response amplitudes. Thus, the combined measurement of ΔR* and ΔR1 in response to oxygenation changes is expected to increase the sensitivity and specificity of oxygen-enhanced MRI.

Conclusion
We consider this method to be a valuable tool for the comprehensive analysis of the complex information delivered by oxygen enhanced MRI for non-invasive tissue oxygenation measurements. Still, further studies need to relate the MR findings with histological results or therapy outcome to prove clinical relevance.

Figure 1
a) and b) anatomical reference scans. c) (ΔR*, ΔR1) scatter plot, depicting all voxels with their ΔR1, against - ΔR* response amplitude. green: reference voxels, red: all other voxels. d) non-normoxic response map, depicting voxels that are located in the non-normoxic section in c): red: voxels outside the reference tissue region (area in transparent green), green: reference tissue voxels classified as outlier by cluster analysis. The other two patients of this study (glioblastoma, lymphoma) did not show any significant enhancement in their outlier maps.