Novel MR method to detect non-normoxic tissue based on cluster analysis of the dynamic R_2* and R_1 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 R_2* or R_1 relaxation rates to oxygen-enhanced respiratory challenges. The observed changes are expected to reflect the level of blood oxygenation (ΔR_2*) and of dissolved oxygen in plasma and tissue (ΔR_1). Results are mostly presented as ΔR_1 or ΔR_2* response maps [1-7], by graphical representations of the dynamic ΔR_1 or ΔR_2* response over time [3,7], or by (ΔR_2*, ΔR_1) 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_2*, ΔR_1) 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_1 and ΔR_2* 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_1 and ΔR_2* 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 ΔR_1 and ΔR_2* to an oxygen enhanced respiratory challenge. The ΔR_1 against ΔR_2* response amplitudes of all voxels are depicted in an (ΔR_2*, ΔR_1) 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_2*, ΔR_1) scatter plot are assumed to be outliers and excluded from further analysis. The lowest ΔR_2* value and the lowest ΔR_1 value of this reference cluster define the threshold for a voxel to be accepted as normal. The voxel with the lowest ΔR_2* value further determines the ΔR_1 threshold. Voxels with an ΔR_2* and ΔR_1 response lower than the 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) after written informed consent was obtained. They all underwent respiratory challenges with 1/4/2min of air/carbogen/air breathing. For simultaneous R_1 and R_2* 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 $R_{1,0}$ and B_1 measurement as previously described [6]: Data were registered and corrected for motion before ΔR_2* was estimated from the multi-echo decay and ΔR_1 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 O_2 or CO_2 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_2* and ΔR_1 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_2* but conspicious ΔR_1 response amplitudes, and also voxels with conspicious ΔR_2* but normal ΔR_1 response amplitudes. Thus, the combined measurement of ΔR_2* and ΔR_1 in response to oxygenation changes is expected to increase the sensitivity and specificity of oxygen-enhanced MRI.

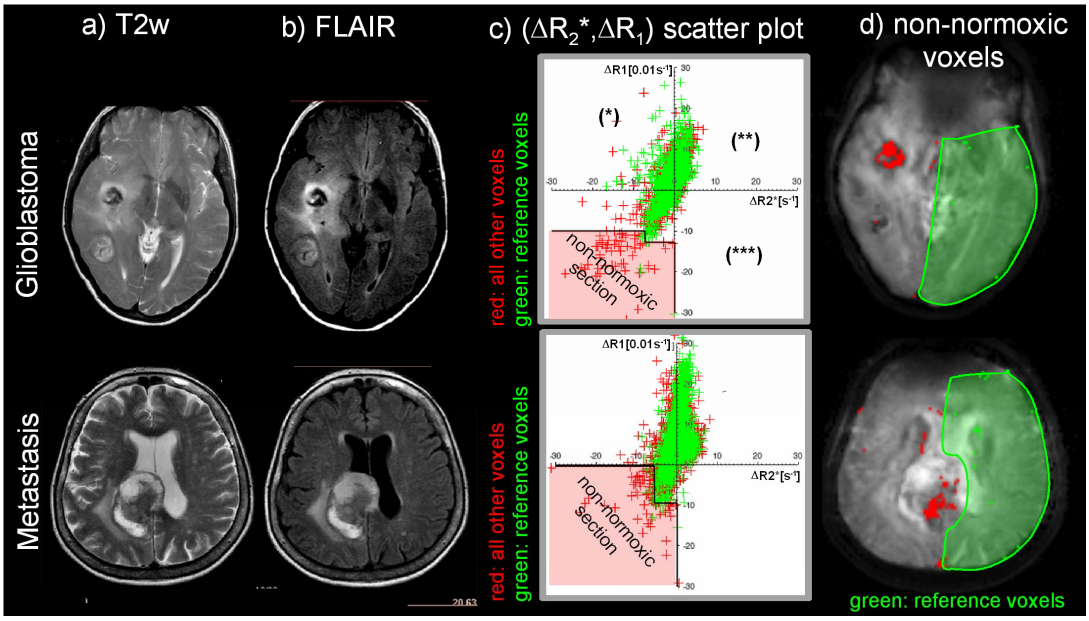

Figure 1

a) and b) anatomical reference scans. c) (ΔR_2*, ΔR_1) scatter plot, depicting all voxels with their ΔR_1 - against - ΔR_2* 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 classifed as outlier by cluster analysis. The other two patients of this study (glioblastoma, lymphoma) did not show any significant enhancement in their outlier maps.

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.

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