# Characterization of Hypoxic Areas in the Human Brain

Nuria Maria Hirsch[1], Christine Preibisch[1,2], Vivien Tóth[1], Jürgen den Hollander[1], Annette Förschler[1], Hendrik Kooijman[3], and Claus Zimmer[1]
[1]*Department of Neuroradiology, Klinikum rechts der Isar der TU München, München, Germany,* [2]*Department of Neurology, Klinikum rechts der Isar der TU München, München, Germany,* [3]*Clinical Application, Philips Healthcare, Hamburg, Germany*

**Introduction:** Hypoxia is assumed to promote the development and proliferation of tumor stem cells especially in highly malignant and aggressive tumors [1]. Techniques for quantifying tissue oxygenation could therefore significantly extend the diagnostic potential of MRI. The presence of paramagnetic deoxygenated hemoglobin in venous vessels causes microscopic susceptibility differences that are visible in *T2** imaging. If additionally tissue vascularization and the hematocrit are taken into account, quantitative information on tumor oxygen saturation can be obtained. In this study, hypoxia was mapped semi-quantitatively from *T2*, *T2** and *CBV* measurements with an emphasis on fast imaging methods that can easily be employed in the clinic.

**Materials and Methods:** According to the theory of Yablonskiy and Haacke, a relation between the fraction of oxygenated blood *Y* and the transverse relaxation times *T2* and *T2** can be derived for a blood vessel network of randomly oriented magnetized cylinders [2]:

$$1 - Y = \frac{R2'}{\frac{4}{3} \cdot \pi \cdot \gamma \cdot \Delta\chi \cdot B_0 \cdot \square} \approx \frac{R2'}{c \cdot CBV} = q$$

where $R2' = 1/T2^* - 1/T2$. $\gamma$ is the gyromagnetic ratio; $\Delta\chi = \Delta\chi_0 \cdot cHct$ is the magnetic susceptibility of blood with $\Delta\chi_0 = 0.264$ ppm being the susceptibility difference between fully oxygenated and fully deoxygenated hemoglobin [3]. Those constants are merged in the constant $c$ which is 317 $sec^{-1}$ for an assumed small vessel hematocrit $cHct$ of 0.42·0.85 [4] at a field strength $B_0$ of 3T. The venous blood vessel fraction □ is approximated by the cerebral blood volume *CBV*. In this work the ratio $q = R2' / (c \cdot CBV)$ is used as an indicator for hypoxia. Imaging was performed on a 3T Philips Achieva (Philips, The Netherlands) with an 8-channel receive head coil and a whole-body transmit coil. *R2'* mapping (voxel size 2x2x3 $mm^3$, matrix 112x106, 30 slices) was performed in 4 healthy subjects (3 m, mean age 33y) and 20 glioma patients (11 m, mean age 54y). *T2** was measured with a multi-gradient echo sequence (12 echoes, $TE_1$ = 6 ms, $\Delta TE$ = 5 ms, *TR* = 1950 ms, □ = 30°, rapid flyback, acq time 3:05 min). *T2** maps were corrected for background gradients [5] and motion artifacts, if necessary [6]. *T2* maps were obtained using a GRASE sequence (8 echoes, $TE_1$ = 16 ms, $\Delta TE$ = 16 ms, *TR* = 8547 ms, acq time 2:16 min). Only the even echoes were fitted to eliminate influences of imperfect RF pulses. In patients, *CBV* maps were obtained by VASO [7] and the DSC method [8]. Data coregistration, fitting and calculation of *q* was performed with SPM8 (www.fil.ion.ucl.ac.uk/spm) and custom programs in Matlab (The MathWorks, Natick, MA, USA); DSC data were evaluated using Stroketool (Digital Image Solutions, Frechen, Germany). $CBV_{DSC}$ was normalized by setting healthy white matter to 1.5%. Since VASO tends to underestimate *CBV* in healthy tissue and overestimates it in areas where the contrast agent leaks to the extravascular space [9], $CBV_{VASO}$ was limited to values between 1.5% and 10%.

**Results and Discussion:** *R2'* maps from healthy volunteers were relatively homogenous with moderate contrast between GM and WM, but increased values in areas with iron deposition or macroscopic magnetic susceptibility gradients. In GM and WM, the subject averages of *T2* were 92.7 ms and 76.4 ms; *T2** amounted to 55.2 ms and 51.1 ms; *R2'* was 7.6 $sec^{-1}$ and 6.4 $sec^{-1}$. Our *T2** values agree well with a recent study on tissue oxygenation whereas our *T2* and *R2'* values are at least 10% higher [10]. Thus, overestimation of *T2* due to RF pulse imperfections [11] is the most likely reason why the average quotient *q* was not restricted to the range [0, 1] as expected by theory.

Nevertheless, the quotient *q* seems to allow a semi-quantitative evaluation of hypoxic areas in gliomas. In 9 patients we found increased values for *q* indicating potentially hypoxic areas either in the contrast enhancing solid tumor or in the non-enhancing infiltration zone. In other cases the hyperintense signal corresponded to tumor necrosis or intratumoral bleeding.

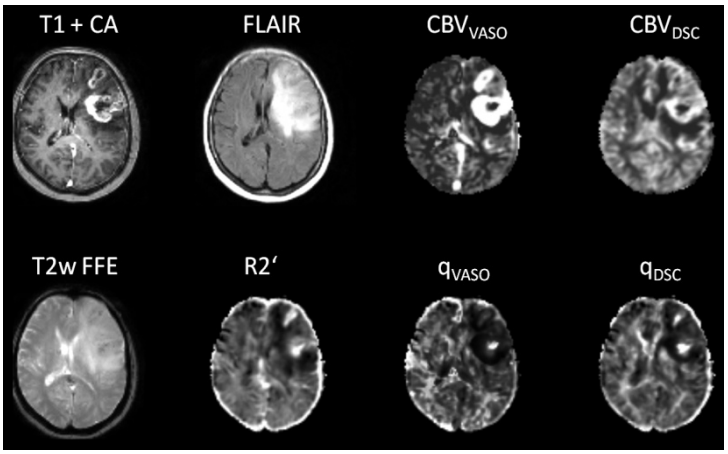


**Figure 1.** Selected slice of a glioma patient. Anatomical images (T1w with contrast agent (CA), FLAIR and T2w fast field echo), *R2'* and *CBV* maps as well as maps of the hypoxia indicator *q* are shown. The $q_{VASO}$ calculated from $CBV_{VASO}$ identifies one potentially hypoxic area within the tumor while $q_{DSC}$ indicates two such areas.

Figure 1 shows a selected slice of a glioma patient. *R2'*, $q_{VASO}$ and $q_{DSC}$ reflect areas of increased susceptibility differences due to increased amounts of deoxyhemoglobin, where the *q* maps are corrected for high vascularization. While $q_{VASO}$ shows one potentially hypoxic area in the tumor, two such areas can be seen in the $q_{DSC}$. This illustrates the problem of *CBV* quantification in areas with contrast agent leakage (see contrast enhanced T1w image for reference). $CBV_{VASO}$ clearly overestimates the real *CBV* and thus largely decreases $q_{VASO}$. The DSC method on the other hand rather tends to underestimate *CBV* [12], which generally increases $q_{DSC}$. Thus, both methods suffer from systematic errors in areas of contrast agent leakage. DSC also requires an arterial input function whose determination can be problematic. Overall, DSC *CBV* mapping turned out to be more robust.

**Conclusion:** Calculating the ratio *q* from *T2*, *T2** and *CBV* provides a method to detect microscopic susceptibility variations and indicate potentially hypoxic areas in the brain. *q* is biased in areas with increased iron content, e.g. in the pallidum, in hemorrhages, or in areas where *R2'* values are unreliable due to macroscopic susceptibility gradients affecting *T2**. However, in combination with anatomical images, hypoxic tumor areas can be detected in this way. To make the method truly quantitative, the values of all required parameters would have to be determined as exactly as possible, which is still somewhat out of scope of a clinical protocol in terms of speed and volume coverage.

**References:** [1] Heddleston JM et al, *Cell Cycle,* 2009; 8:3274-3284 [2] Yablonskiy DA, Haacke EM, *MRM*, 1994; 32:749-763 [3] Spees WM et al, *MRM*, 2001; 45:533-542 [4] An H, Lin W, *JCBFM,* 2000; 20:1225-1236 [5] Baudrexel S et al, *MRM,* 2009; 62:263-268 [6] Magerkurth J et al, *MRM,* 2011; 66:989-997 [7] Uh J et al, *MRM,* 2009; 61:659-667 [8] Ostergaard L, *Top MRI*, 2004; 15:3-9 [9] Lu H et al, *AJNR,* 2008; 29:373-378 [10] Christen T, Zaharchuk G, *Proc ISMRM*, 2011; 19:2728 [11] Majumdar S et al, *MRM,* 1986; 3:397-417, 562-574 [12] Quarles CC et al. *Phys Med Biol,* 2009; 54:5749-5766