Inverse Z-spectrum analysis for clean NOE and amide CEST-MRI – application to human glioma

Moritz Zaiss[1], Johannes Windschuh[1], Jan-Eric Meissner[1], Daniel Paech[2,3], Alexander Radbruch[2,3], and Peter Bachert[1]

[1]Dept. Medical Physics in Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [2]Dept. of Neuroradiology, University of Heidelberg, Heidelberg, Germany, [3]Section Neuro–oncologic Imaging, German Cancer Research Center (DKFZ), Heidelberg, Germany

Purpose Endogenous chemical exchange saturation transfer (CEST) effects are always diluted by competing effects such as direct water saturation and semi-solid magnetization transfer (MT). This leads to unwanted T_2 and MT signal contributions that dilute the observed CEST signal (spillover effect)[1,2]. Furthermore, all CEST effects appear ~~also~~ to be scaled by the T_1 relaxation time of the mediating water pool[2,3]. As MT, T1 and T2 are also altered in tumor regions, a recently published correction algorithm yielding the apparent exchange-dependent relaxation AREX, is used to evaluate *in vivo* CEST effects[2]. This study focuses on CEST effects of amides (3.5 ppm) and Nuclear-Overhauser-mediated saturation transfer (NOE, -3.5 ppm) in human glioblastoma.

Methods Three male patients with newly diagnosed and histologically proven glioblastoma were enrolled in this prospective study before surgery. Approval of the local ethics committee after written informed consent was obtained. CEST contrast was acquired with a centric reordered gradient-echo sequence (~4 min) at $B_0 = 7$ T employing a 24-channel head coil. Presaturation (4.2s) consisted of 140 inversion pulses (t_p=15ms, t_d=15 ms, DC=50 %, B_1=0.8 μT) applied at 66 offsets from −100 ppm to 100 ppm with adaptive sampling (higher at +-3.5 ppm). T1 mapping was achieved by fitting T1 weighted images of a saturation recovery GRE with 10 different recovery times from 1s to 5s. Z-spectra were fitted pixel-wise by a multi-Lorentzian fit which yields a label (Z_{lab}) and a reference Z-spectrum (Z_{ref}) for each CEST effect. The spillover, MT and T1 corrected AREX-map was calculated pixel-wise by:

$$AREX= (1/Z_{lab}-1/Z_{ref})/T_1 \qquad (1)$$

The uncorrected Lorentzian difference[4] evaluation MTR_{LD} was generated by

$$MTR_{LD} =Z_{ref}-Z_{lab} \qquad (2)$$

Results The contrast of NOE and amide CEST maps is significantly altered for AREX evaluation compared to MTR_{LD} (Fig 1c-f). The Gd-enh. fusion with $MTR_{LD,amide}$ (c) clearly delineates the ring tumor enhancement with central necrosis but also the periventricular diffuse contrast enhancement; the tumor shape appears similar as delineated by the T1 map. $AREX_{amide}$ is hypointense in the necrosis and hyperintense in the diffuse enhancement but shows no significant correlation with the ring enhancement. $AREX_{amide}$ shows overall less GM/WM contrast compared to MTR_{LD} but shows a hotspot near the diffuse enhancement. The NOE effect evaluated by MTR_{LD} shows slight hypointensity in the necrosis and a weak GM/WM contrast. $AREX_{NOE}$ shows a very clear drop in the tumor necrosis and also a slight decrease in the whole enhancement region compared to contralateral tissue. Interestingly, the GM/WM contrast of $AREX_{NOE}$ is very strong. Similar outcomes were observed in the 2 other patients (not shown).

Discussion Both, the change of contrast due to AREX correction but also the contrast within the T1 map indicates that spillover and T1 correction is important for interpretation of CEST effects in glioblastoma[3]. The $AREX_{amide}$ map is more homogeneous than the uncorrected map. As CEST effects of amides are a function of pH[5,6], homogeneous contrast is expected. Due to the similar shape of the tumor in $MTR_{LD,amide}$ and T_1 maps the hyperintensity could actually be a T1 shine-through, nevertheless the uncorrected APT shows the clearest tumor delineation. The hotspot in $AREX_{amide}$ could not be further characterized as it did not show up on other contrasts. For the NOE the higher GM/WM contrast makes sense since dipolar interactions depend on the tissue viscosity and restriction of proteins. The drop in tumor and necrosis remains unclear, speculations consider lower protein content[4] or unfolding of proteins[7].

Conclusion

In vivo NOE and amide CEST effects can be properly isolated at 7T. Spatial variations of spillover and T_1, due to heterogeneities of glioblastoma, can easily be corrected by AREX post process. Thus, clean NOE and amide CEST maps can be obtained within 5 minutes providing novel and unbiased insight into properties of tumors on a molecular level.
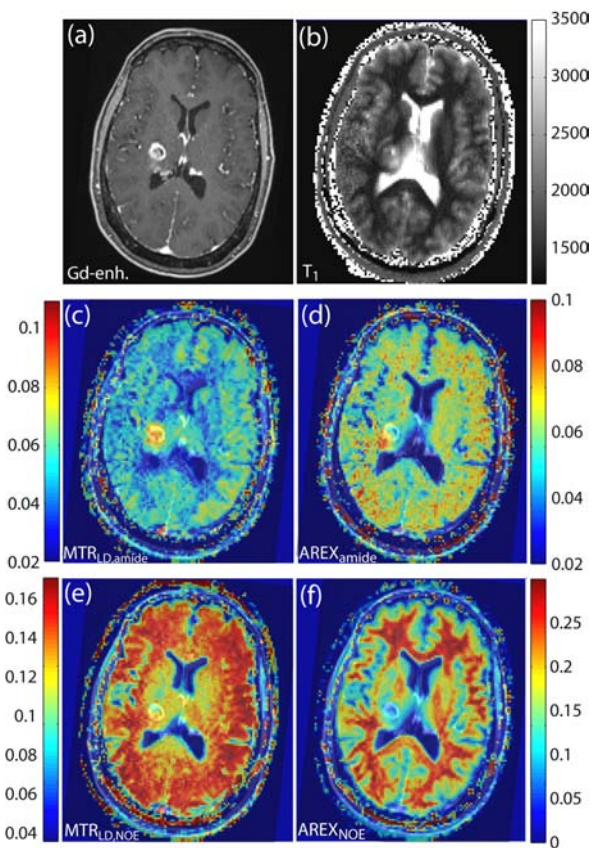

Figure 1: Gd–enhanced image shows the typical ring enhancement with diffuse enhancement below the tumor (a). Fusion of NOE (c,e) and amide (d,f) CEST maps (colored) and Gd.-enh. images (bw) are shown for uncorrected MTR_{LD} (c,e) and corrected AREX maps (d,f). The AREX correction changes the contrast significantly.

References

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