Mapping Elevated Lactate Levels after Ischemic Stroke using PROBE CEST/NOE: A Feasibility Patient Study at 3T

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Introduction

A novel high-resolution acquisition and post-processing procedure is introduced. It permits the direct observation of disease-associated metabolic changes in brain tissue. In particular, an identification of ischemic regions is achieved via mapping the local lactate (Lac) concentration by means of chemical exchange saturation transfer (CEST) [1] and the nuclear Overhauser effect (NOE) [2]. The feasibility of an application of the recently developed *Prospective Baseline Enhancement (PROBE)* [3,4] method *in vivo* is demonstrated in healthy subjects and patients suffering from ischemic stroke. With PROBE, confounding background signal from healthy white matter (WM) is compensated, which allows to resolve three distinctive resonances of Lac in the CEST/NOE Z-spectrum [7,8,20] as a biomarker for ischemia [5,6]. The acquisition scheme was tailored to fit into a clinical setting at 3 T, whereas most current applications of CEST/NOE in human studies have been performed at 7 T.

Methods

Physiological Background—Background signal from healthy WM, leading to a broad and slightly structured Z-spectrum baseline (BL), can be modeled as a three pool spin system at 3 T (more individual contributions become perceptible at higher B_0) [8-16]. Besides macromolecular magnetization transfer (MT), there is also an aliphatic contribution at ~ 3.5 ppm (via NOE [8,15]). This work investigated the *in vivo* applicability of PROBE with particular focus on Lac. Under ischemic conditions, O_2 deficiency upregulates anaerobic glycolysis resulting in the accumulation of Lac [17,18]. Three saturation transfer pathways can be utilized for a detection of elevated Lac levels (Fig. 1) [14,20]. Due to compensation of confounding background in Z-spectra via PROBE, a detection of all three Lac resonances becomes feasible.

Basic Principle—In PROBE, a background spin system is modeled from a scout Z-spectrum acquisition (i.e. a standard Z-spectrum) for a tissue of reference. An MR-sequence-specific optimization (via an optimal-control, matrix-algebra-based calculation [21,22]) yields a bespoke set of saturation power amplitudes, $\omega_{1,max}(\Delta\delta)$, for each saturation offset $\Delta\delta$ [3,19]. In the optimization process of $\omega_{1,max}(\Delta\delta)$, signal intensity is treated as a function of $\Delta\delta$ and baseline is modulated, such that it matches a particular $I_{target} = \text{const.}$ (Fig. 2).

Acquisition Details—Suitable saturation pulse amplitudes for PROBE were calculated based on WM Z-spectra of three healthy subjects (22-29y; 2F/1M) recorded at 3T (MAGNETOM Prisma [*]). $\omega_{1,max}(\Delta\delta)$ was optimized for a flat baseline, $I_{target}(\Delta\delta) = 0.8 \times I_0$ (Fig. 2). In total, 8 stroke patients (51-88y; 5F/3M) were recruited after ischemic stroke, as part of a prospective observational trial (LOB-BBB, NCT02077582), which had been approved by the local Ethics Committee. MRI (3T; MAGNETOM TIM Trio [*]) included FLAIR, DWI and T_2^* -weighted imaging on days 1&2. PROBE Z-spectra were acquired in an extra session on days 2-4, including a short anatomical scan and B_0 mapping. 2D saturation-prepared GRE images were acquired with $\alpha = 78^\circ$, TR/TE = 200/7.1 ms, 100 ms Gaussian saturation pulse, RF and gradient spoiling, nominal voxel resolution $0.9 \times 0.9 \times 4 \text{ mm}^3$. 18 saturation offsets, $\Delta\delta$, were acquired (plus 2 reference images without saturation (I_0) for signal drift correction and normalization), resulting in $TA = 18$ min. Transmit frequency was adjusted regularly. Two different approaches were tested for saturation offset sampling: in both schemes, offsets were sampled around Lac peaks at $\Delta\delta = -0.7$ and -3.5 ppm (-CH and $-\text{CH}_3$ groups, respectively). Scheme A included a redundant sampling around -3.5 ppm, whilst scheme B employed dense sampling in the vicinity of the $-\text{CH}_3$ peak. In addition 0.8 ppm (-OH group) was detected in scheme A. For comparison, densely sampled PROBE Z-spectra were obtained from 3 healthy subjects ($\Delta\delta$ within ± 5 ppm, 0.1 ppm spacing).

3 Optimized $\omega_{1,max}(\Delta\delta)$

Postprocessing—A schematic overview on the post-processing pipeline is depicted in Fig. 4. Both sampling schemes underwent a similar retrospective correction. All PROBE Z-spectra were retrospectively corrected against B_0 inhomogeneities. The redundant sampling scheme A permitted a selection of images with the lowest level of motion artifacts around -3.5 ppm, whereas a more reliable $\text{Lac}_{\text{contrast}}$ could be calculated for the more densely sampled scheme B. Generally, $\text{Lac}_{\text{contrast}}$ was computed as mean signal intensity difference between BL offsets and Lac peak positions. Particularly for scheme B, Lorentzian peak fitting became possible at $\Delta\delta = -3.5$ ppm.

Whilst offsets $\Delta\delta$ affected by motion artifacts, were excluded via absolute deviation thresholding against a mean BL-image, maps of $\text{Lac}_{\text{contrast}}$ only depict patches of voxels, where all peaks included in $\text{Lac}_{\text{contrast}}$ reached beyond threshold r .

References

- Ward et al., JMR, 143 (2000) 79.
- Overhauser, Phys. Rev., 92 (1953) 411.
- Lenich et al., Music City CEST, Nashville, TN, USA, 2017.
- Lenich et al., ISMRM, Honolulu, HI, USA 2017, pp. 3780.
- Gillard et al., Am. J. Neurorad., 17 (1996) 873.
- Harston et al., Brain, 138 (2015) 36.
- Govindaraju et al., NMR in Biomed., 13 (2000) 129.
- Van Zijl et al., Neuroimage, 168 (2018) 222.
- Zhang et al., MRI, 34(8) (2016) 1100.
- Zhang et al., MRM, 78(3) (2017), 881.
- Xu et al., MRM, 71(5) (2014) 1798.
- Zu et al., MRM, 72 (2) (2014) 471.
- Liepinsh et al., MRM, 35(1) (1996) 30.
- DeBrosse et al., Sci. Rep. 6 (2016) 19517.
- Brooks et al., MRM 31(3) (1994) 331.
- Jones et al., Neuroimage, 77 (2013) 114.
- Gatenby et al., Nat. Rev. Cancer, 4 (11) (2004) 891.
- Raichle, Ann. Neurol., 13 (1) (1983) 2.
- Clark et al., MRM 76 (2016) 826.
- Swanson, JMR, 135 (1998) 248.
- Lenich et al., ISMRM, Toronto, ON, Canada (2015), pp. 3347.
- Müller et al., JMR, 230 (2013) 88.
- Petroff et al., Neurology 42 (7) (1992) 1349.
- Taylor et al., NMR in Biomed., 28(11) (2015) 1357.
- Bruhn et al., MRM, 9(1) (1989) 126.
- Jokivarsi et al., MRM, 57 (4) (2007) 647.
- Ewing et al., MRM 41(4) (1999) 696.
- Ordidge et al., MRI, 9(6) (1991) 895.
- Pui, MRI, 12(3) (2000) 395.
- Eliassen et al., Topics in Stroke Rehab., 15(5) (2008) 427.
- Siemens Healthineers, Erlangen, Germany.

1 System Model for Human WM

2 PROBE Acquisition Scheme

4 Post-Processing Pipeline

Results

PROBE Z-spectra were simulated for the optimized saturation power scheme using a healthy WM spin system plus additional Lac. The result with highlighted sampling points for both schemes A & B is depicted in Fig. 5. In Fig. 6, a detailed analysis for various contrasts, obtained from a single PROBE acquisition, was conducted for a healthy subject and an MCA stroke patient (sampling B). MT contrast (MTC) was calculated from mean BL signal $\Delta(I/I_0)_{BL}$. MTC and $\text{Lac}_{\text{contrast}}$ maps exhibit differences between ischemic and healthy regions.

While scheme A (Fig. 6) possesses higher specificity with regards to Lac, sensitivity could be increased for the $-\text{CH}_3$ peak at $\Delta\delta = -3.5$ ppm by using scheme B. Hyperintense patches in $\text{Lac}_{\text{contrast}}$ maps coincide with conspicuous regions in DWI Trace reference images (slice positions are not identical between 1st and 2nd column in Fig. 7; T_2^* map shown in background of $\text{Lac}_{\text{contrast}}$ maps). PROBE acquisitions in 4/8 stroke patients yielded similar Lac mapping results, 1 subject (ACA stroke) remained unobtrusive, whilst datasets of three patients were heavily corrupted by motion artifacts. BL-corrected, ROI-averaged PROBE Z-spectra appear similar as predicted by simulations (Fig. 5).

5 Simulated PROBE

Z-Spectrum with Lac

Discussion & Conclusion

Though B_0 -induced distortions to the baseline in PROBE Z-spectra were addressed and retrospectively look-up corrected [3], ΔB_0 also affects the offset positions and intensity of metabolite peaks. The sparsely sampled schemes in a clinical setting did not allow for an appropriate correction of such. However, the presumably strong increase in Lac following ischemia [5,23-26] led to detectable changes in PROBE Z-spectra. PROBE achieved an improved depiction of individual metabolite signals and baseline changes related to pathology in comparison to previously published "asymmetry-based" CEST techniques (requiring symmetric offset sampling and suffering from overlap). In this preliminary study, it was shown that the PROBE approach can potentially be used for an identification of infarcted tissue. Whilst strong changes in MTC [27-29] (calculated as deviation in mean BL-signal) were observed in a broad region, coinciding almost completely with prominent regions in DWI Trace reference images, hyperintense $\text{Lac}_{\text{contrast}}$ remained limited to narrower areas adjacent or within such [5,30]. The feasibility for an *in vivo* application in a clinical setting at 3 T was successfully demonstrated.

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