ERETIC-based glycogen quantification using SNR-enhanced and localized 13C MRS

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Introduction

In *in vivo* 13C NMR spectroscopy glycogen has been the metabolite of major interest, in particular for studies involving patients suffering from diabetes mellitus. While the combination of proton decoupling and NOE (Nuclear Overhauser Effect) enhancement became the state of the art method for glycogen quantification, localization has been hardly applied due to the low intrinsic sensitivity of 13C MRS. As a consequence subcutaneous lipid signal caused strong baseline distortions, which hampers quantification precision. Absolute quantification using the internal water reference method is not reliable for 13C MRS due to significant differences in B1 homogeneity for 1H and 13C over a large field of view and creatine as internal reference is also not reliable due to changes induced in pathological conditions [3]. ***In this work***, we thus combine ISIS-localized NOE and proton decoupling for SNR enhancement to detect glycogen in human calf muscle. The ERETIC (Electric REference To access In vivo Concentration) [4, 6] signal was used as a synthetic reference standard for quantification. Reproducibility tests regarding the quantified signal intensities, SNR enhancement factors and ERETIC signal stability show that quantitative signal-enhanced and localized glycogen detection using the ERETIC method is applicable to physiological studies.

Materials and Methods

A modified ERETIC setup [4, 6] tuned to 32.1MHz was installed on a dual-tune 13C/1H volume calf coil (RAPID Biomedical GmbH) and connected to a Philips Achieva 3T human MRI scanner. The ERETIC loop was placed as close as possible to the 13C coil in order to maximize mutual coupling between the loop and the receive coil and the loop size was minimized to avoid direct coupling with the patient load. From the scanner console the ERETIC pulse shape was set to an exponential Lorentzian; amplitude, phase, decay time and frequency were set with respect to the glycogen signal intensity in the 13C muscle spectra, as shown in Figure 2. ISIS localization was applied with RF pulse centre frequencies on C1 of glycogen. Voxels were placed such that subcutaneous lipids could be avoided. NOE saturated the protons and transferred partial polarization to C1 1ms before the selective inversion in ISIS. Continues wave narrow-band decoupling centred at 5.4 ppm in 1H spectra was applied during acquisition, which collapsed the doublet into a single peak and further increased the C1 signal intensity of glycogen at 100.5 ppm. The decoupling power delivered to the coil was 64W ensuring a fully decoupled C1 peak. Volume based 2nd-order FASTERMAP shimming was applied comprising only the even muscle area and exclusive fat or bone. The reproducibility of SNR enhancement and the stability of ERETIC during SNR enhancement were assessed by single comparative experiments on seven subjects (two male and five female, age = 27±4 years, weight = 71±15 Kg) and with twelve repetitive experiments on one subject (male, 29, 90Kg) (different measurement time on 5 different days). In addition, glycogen/ERETIC ratios were determined from 4 repetitive measurements performed consecutively in the same volunteer. In each experiment, two sequences were performed, one with and the other one without NOE and decoupling enhancement. 512 sample points, 4096 averages were used. The repetition time was 121ms for the first sequence and 550ms for the enhanced sequence due to the SAR restrictions for proton decoupling; resulting in a scan time of 15min and 40min respectively. The ERETIC reference signal was enabled in all experiments. The acquired two spectra were fitted using TDFDfit [5] [Figure 2] and the enhancement ratios and ERETIC signals with and without enhancement were compared among all the experiments.

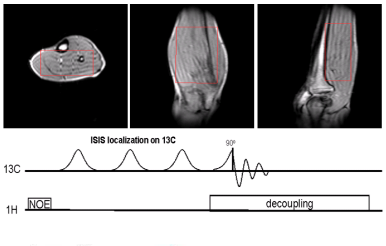

Figure 1 *(top) Voxel of interest in the calf muscle; (bottom) acquisition sequence combining ISIS, NOE& decoupling enhancement.*

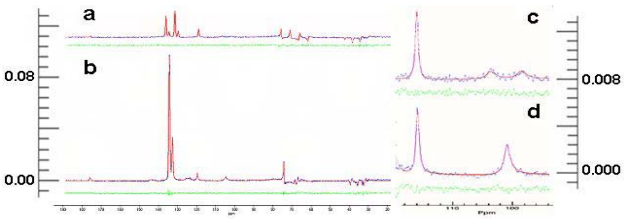

Figure 2 *Calf muscle 13C spectra (blue), fitting (red) and residual (green): (a), direct acquisition; (b), with NOE and proton decoupling; (c), spectra from (a) enlarged 90-120ppm; (d), spectra from (b) enlarged 90-120ppm. (a) and (b), (c) and (d) are on the same scale, respectively. The ERETIC reference appears at 115ppm, glycogen peaks are centered at 100.5ppm.*

Results and Discussion

Glycogen in calf muscle was detectable in all subjects. During all the measurements on seven subjects and twelve measurements on the same subject, we observed that ERETIC and enhancement worked without failure. Subcutaneous fat did not cause baseline distortions due to the localization. The ERETIC and glycogen signal intensities were calculated from spectral fitting results in order to get a precise enhancement and stability evaluation. The enhancement factors obtained in the same subject are plotted in Figure 3 (a), with the slope indicating the enhancement ratio. The average enhancement was 3.45±0.43. Similarly the enhancement on five different subjects was plotted in Figure 3 (b). The enhancement was 3.53±0.48 among the subjects (including 5 out of 7 data sets that fulfilled fitting quality criteria given by CRLB < 30%). The remaining deviation resulted from the potential error in the spectra fitting step, especially for low signal intensities in the non-enhanced spectra. The largest error was at 45.67% while the average was still 23.89%. In the enhanced spectra this fitting error was reduced to the average of 9.91%, with the largest being only 15.57%. Good shimming was also a key issue in glycogen detection since broader linewidth in the original spectra worsened the fitting and quantification. The FWHM (Full Width at Half Maximum) was around 25Hz. Thus ISIS localized SNR enhancement proved to be reproducible and could improve the quantification accuracy. The ERETIC intensities in the original and enhanced 13C spectra are plotted in Figure 3 (c). ERETIC intensities determined with TDFDfit [5] with and without enhancement were 5.87±0.31 and 5.88±0.58 (n = 17, p = 0.81) for all the 17 experiments and thus equal. Enhanced glycogen/ERETIC ratio in normalized volume size from 4 consecutive experiments in the same volunteer was 0.76±0.03.

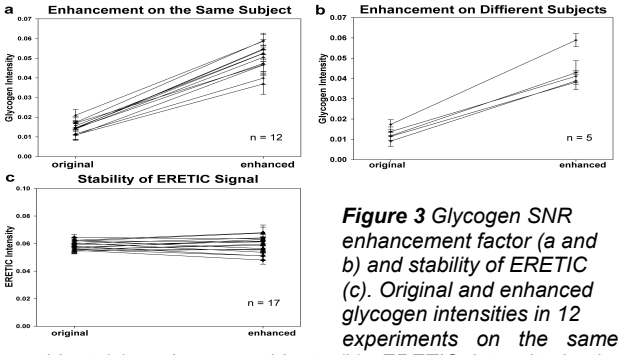

Figure 3 *Glycogen SNR enhancement factor (a and b) and stability of ERETIC (c). Original and enhanced glycogen intensities in 12 experiments on the same subject (a) and on 7 subjects (b). ERETIC intensity in the original and enhanced spectra (c). Each point was plotted with the fitting error as standard deviation. The straight line connects the same experiment or the same subject. The slope of line indicates the enhancement factor. The y axis is scaled to a arbitrary range.*

In conclusion the combination of NOE and decoupling can enhance the glycogen signal at a reproducible level and enables higher fitting and thus quantification reliability. As ERETIC signal stability proved to be unaffected by SNT enhancement and ISIS localization is robust, it is promising to use the ERETIC signal as reference for absolute quantification based on localized 13C MRS among different subjects and experiments.

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