Uncovering Long Range J-coupled Lipid Resonances in Human Calf In-Vivo: Pilot Findings Using Localized Two Dimensional Total Correlated Spectroscopy

Manoj K Sarma[1], Andres Saucedo[1], Christine H Darwin[2], Cathy C Lee[2,3], Ravinder R. Regatte[4], and M. Albert Thomas[1]

[1]Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States, [2]Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States, [3]Greater Los Angeles Veterans Affairs Medical Center, Los Angeles, CA, United States, [4]Center for Biomedical Imaging, New York University School of Medicine, New York, NY, United States

Synopsis

Based on the same principle of localized correlated spectroscopy (L-COSY) of coherence transfer during mixing period, total correlated spectroscopy (TOCSY) is a powerful technique that can provide correlations for both direct and long range coupled spins via relayed coherence transfer. Due to the SAR issue, the potential of TOCSY has not been fully exploited *in-vivo* and only few versions of TOCSY have been evaluated in brain. Here we have implemented a novel version of localized TOCSY technique for implementation in human calf muscle *in-vivo*, and compared results from three mixing strategies. Results are presented from a corn oil phantom, and in-vivo 2D spectra from 4 healthy volunteers and 1 diabetic patient obtained on 3T clinical platforms. We demonstrated that TOCSY can uncover the hidden relayed peaks, particularly that of IMCL/EMCL in calf muscle which can play an important role in better estimation of degree of unsaturation.

Introduction:

Localized correlated spectroscopy (L-COSY)[1] facilitates improved detection of overlapping metabolites with increased spectral dispersion. In skeletal muscle, COSY has been used to separately assess saturated and unsaturated lipid components, allowing estimation of the degree of unsaturation[2,3]. Based on the same principle of COSY, total correlated spectroscopy (TOCSY)[4] is another powerful technique that contains information about the directly scalar coupled spins coherence transfer. However, TOCSY can provide additional correlations for remotely J-coupled spins and exhibits an in-phase magnetization transfer. *In-vivo* 1D spectral-editing TOCSY[5,6] and localized 2D TOCSY[7] in human brain have been demonstratedn previously. Due to the SAR issue associated with the requirement of a sustained train of RF pulses during TOCSY mixing, the potential of TOCSY has not been fully exploited *in-vivo*. Here, we propose a novel version of localized TOCSY technique to recover hidden resonances in human calf muscle *in-vivo*. We also compare the results from three mixing strategies: a spin lock scheme using continuous wave (CW) RF pulses[8,9], an MLEV4[10] scheme, and a CW spin lock scheme with composite pulses.

Materials and Methods:

Fig.1 shows the schematic diagram of the TOCSY sequence. TOCSY block does not contribute to the echo time and the total echo time is nothing but the echo time of the PRESS localization block. The time between the last 180° refocusing pulse in the PRESS localization and the TOCSY block was incremented to introduce the t_1 evolution. Global water suppression was performed using a WET[11] scheme, preceding the first excitation pulse. To test the sequence, a corn oil phantom was used. The sequence was further evaluated in the calf muscle of four healthy volunteers (age, 23-40 years) and one type 2 diabetic subject (63 years). All data were collected on a 3T Prisma MRI scanner using a 15 channel knee 'transmit/receive' coil. The TOCSY acquisition parameters for the phantom and in-vivo calf muscle were: a voxel size of 4x4x4cm^3, TE=30ms, TR=2-2.5s, averages=8, 64 Δt_1 increments with 0.8ms, 1024 t_2 points, F_1 and F_2 bandwidths of 1250 Hz and 2000 Hz respectively with scan time ~17-25min. 2D L-COSY spectra were also acquired with same parameter for comparisons purposes. Acquired data were extracted, and post-processed[12] with a library of custom MATLAB-based program.

Results:

Fig. 2 shows our initial results in corn phantom showing spectra recorded with L-COSY and TOCSY using the three different mixing strategies. Cross peaks of all lipid multiplets were well visible and separated from the main diagonal. Due to in-phase coherent transfer the multiplet structure of each cross peak is more apparent in TOCSY spectra. Relayed cross peaks of intramyocellular (IMCL)/extramyocellular lipids (EMCL) are visible in TOCSY spectra which cannot be detected in COSY. TOCSY spectra measured with the three mixing strategies at different mixing time are shown in Fig. 3. At very short mixing time of 11.5ms also TOCSY with SL showed relayed cross peaks. Fig. 4 demonstrates results obtained at 3T from a patient with diabetes. The relayed cross peak of IMCL/EMCL which are not visible on COSY (Fig. 4(B)), can be observed in TOCSY with SL at mixing time 11.5ms and TOCSY with MLEV-4 at mixing time 45ms (Fig. 4(C) and 4(D)). TOCSY with MLEV-4 spectra recorded in a healthy volunteer are shown in Fig. 5. A projected spectrum along the F_1 dimension from the same voxel is included for comparison. Here also, relayed cross peak of IMCL/EMCL are visible demonstrating the reliability of the TOCSY technique.

Discussion:

Although different versions of TOCSY have been implemented before for in-vivo brain study, this work represents the first demonstration of a robust *in vivo* TOCSY for calf muscle application. Although COSY spectra have a higher SNR than TOCSY due to the fact that the optimum mixing conditions for TOCSY are harder to realize *in-vivo* within SAR limits, we demonstrated that TOCSY can uncover the hidden relayed cross peaks, particularly that of the unsaturated IMCL/EMCL in calf muscle which can play an important role in clinical application in diabetic/obese skeletal muscle studies for better estimation of degree of unsaturation. Compared to COSY, TOCSY has the advantage of eliminating signal cancellation and improving spectral resolution with pure absorptive phase-sensitive crosspeaks[7]. Even though CW-SL performed better, MLEV based TOCSY may be a better option at 3T due to less SAR compared to the CW pulses allowing it to use in other body parts. There are still some limitations to the work including the long scan time, which will be addressed in future studies.

Conclusion:

While these initial results are promising, further optimization and validation with a larger pool of subjects is needed. We expect that the new developments presented in this work will facilitate in-vivo applications of TOCSY in clinical evaluations.

Acknowledgements

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References

1. Thomas MA, Yue K, Binesh N, et al. Localized two-dimensional shift correlated MR spectroscopy of human brain. Mag Res Med 2001; 46(1):58–67.

2. Velan SS, Said N, Durst C, et al. Distinct patterns of fat metabolism in skeletal muscle of normal weight, overweight and obese humans. Am J Physiol Regul Integ Comp Physiol 2008;295(4): R1060–R1065.

3. Velan SS, Durst C, Lemieux SK, et al. Investigation of muscle lipid metabolism by localized one- and two-dimensional MRS techniques using a clinical 3T MRI/MRS scanner. J Magn Reson Imaging 2007;25(1):192–199.

4. Braunschweiler L, Ernst RR. Coherence Transfer by Isotropic Mixing: Application to Proton Correlation Spectroscopy. J Magn Reson 1983;53(3):521–528.

5. Choi IY, Lee SP, Shen J. Selective homonuclear Hartmann-Hahn transfer method for in vivo spectral editing in the human brain. Magn Reson Med 2005;53(3):503–510.

6. Marjanska M, Henry PG, Bolan PJ, et al. Uncovering hidden in vivo resonances using editing based on localized TOCSY. Magn Reson Med 2005;53(4):783-789.

7. Andronesi OC, Ramadan S, Mountford CE, Sorensen AG. Low-power adiabatic sequences for invivo localized two-dimensional chemical shift correlated MR spectroscopy. Magnetic Resonance in Medicine 2010; 64(6):1542–1556.

8. Zu Z, Li H, Jiang X, Gore JC. Spin-lock imaging of exogenous exchange-based contrast agents to assess tissue pH. Magn Reson Med 2017. [Epub ahead of print]

9. Sharafi A, Xia D, Chang G, Regatte RR. Biexponential T1ρ relaxation mapping of human knee cartilage in vivo at 3 T. NMR Biomed 2017;30(10).

10. Brittain JH, Hu BS, Wright GA, et al. Coronary Angiography with Magnetization-Prepared T2 Contrast. Magn Reson Med 1995; 33(5):689–696.

11. Ogg RJ, Kingsley PB, Taylor JS. WET, a T1- and B1-insensitive water-suppression method for in vivo localized 1H NMR spectroscopy. J Magn Reson B 1994;104(1):1–10.

12. Sarma MK, Huda A, Nagarajan R, et al. Multi-dimensional MR spectroscopy: towards a better understanding of hepatic encephalopathy. Metab Brain Dis 2011;26(3):173–184.

Figures

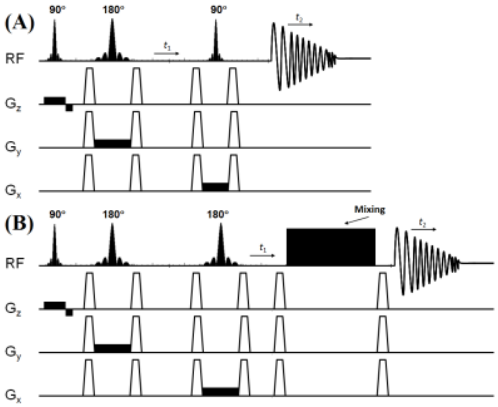

Fig. 1: Schematic representation of the **(A)** COSY and **(B)** TOCSY sequence. For TOCSY, the basic COSY sequence with a [90°–180°–Δt1–90°–Acquisition] scheme for localization was modified as [90°–180°–180°–Δt1–TOCSY(Mixing)–Acquisition]. While for COSY the mixing happens during the t_1 evolution which is free of RF pulses, for TOCSY the mixing period is realized under the action of a train of RF pulses right after t_1 evolution.

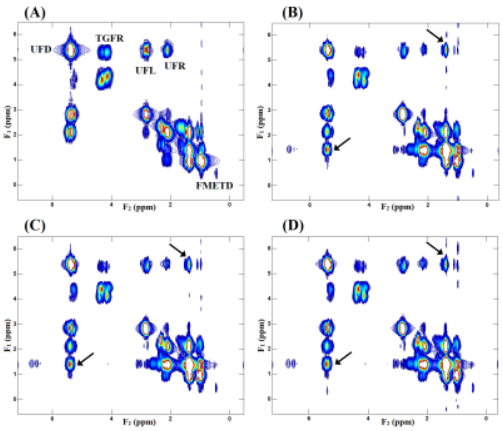

Fig. 2: Example of 2D spectra obtained at 3T in a corn oil phantom using **(A)** L-COSY, **(B)** TOCOSY with MLEV4 (mixing time 45ms), **(C)** TOCSY with spin lock (mixing time 11.5ms), and **(D)** TOCSY with composite spin lock (mixing time 11ms) sequences. Relayed crosspeaks present only in TOCSY are indicated by black arrowheads. The same contour levels are displayed. Peaks are labeled as, UFD=Olefinic fat, TGFR= Triglyceryl fat cross peak, UFR=Unsaturated fatty acid cross peaks right, UFL=Unsaturated fatty acid cross peaks left, FMETD = Methyl fat.

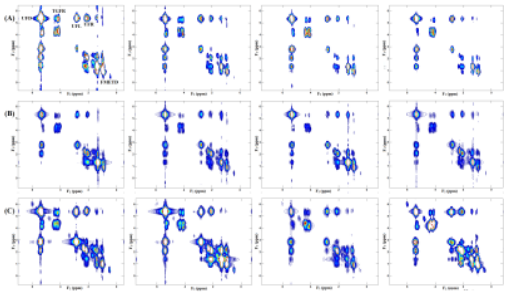

Fig. 3: Comparison of TOCSY spectra with the three different strategies at four different mixing times. **(A)** TOCSY with SL at mixing time of 11.5ms, 51.5ms, 76.5ms, 101.5ms; **(B)** TOCSY with composite SL at mixing time of 10ms, 50ms, 75ms, 100ms; and **(C)** TOCSY with MLEV4 at mixing time of 33ms, 45ms, 85ms, 125ms.

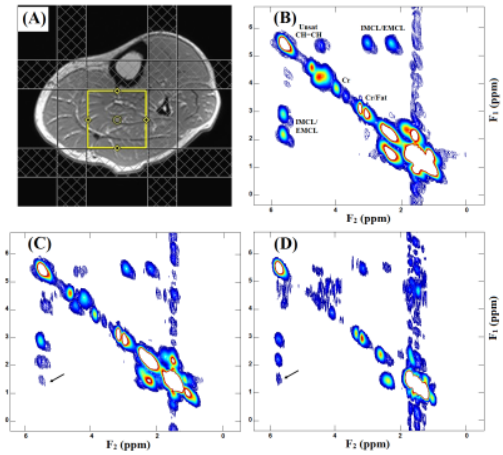

Fig. 4: In-vivo 2D spectra obtained at 3T with the **(B)** L-COSY, **(C)** TOCSY with SL (mixing time 11.5ms), **(D)** TOCSY with MLEV4 (mixing time 45ms) from a 63 years' type-2 diabetic patient in the soleus region as shown in **(A)**. Relayed crosspeaks of IMCL/EMCL seen in corn phantom in TOCSY can be seen here too (indicated by black arrowheads). Cr, creatine; IMCL, intramyocellular lipid; EMCL, extramyocellular lipid.

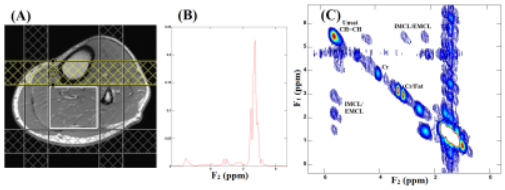

Fig. 5: In-vivo 2D TOCSY-MLEV4 spectrum obtained at 3T from a 40 years healthy control in the soleus region (shown in **(A)**). The 1D spectrum corresponding to the projection along the t1 direction is shown in **(B)**. The 2D TOCSY-MLEV4 spectrum is shown in **(C)**. The same acquisition parameters as used in the diabetic patient (Fig. 4) were used.