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NOTE

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Application of a BIlinear Rotation Decoupling (BIRD) filter in combination with J-difference editing for indirect ^{13}C measurements in the human liver

Pandichelvam Veeraiah[1] | **Kim Brouwers**[1] | **Joachim E. Wildberger**[1] | **Vera B. Schrauwen-Hinderling**[1,2] | **Lucas Lindeboom**[1,2]

[1]Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

[2]Department of Nutrition and Movement Sciences, Maastricht University, Maastricht, The Netherlands

Correspondence
Vera B. Schrauwen-Hinderling, Department of Nutrition and Movement Sciences and Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, P.O. BOX 616, 6200MD, Maastricht, The Netherlands.
Email: v.schrauwen@maastrichtuniversity.nl

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Purpose: Recently, we introduced a quantum coherence based method (ge-HSQC) for indirect ^{13}C-MRS in the liver to track ^{13}C-labeled lipids into the hepatic lipid pool in vivo. This approach is more robust in case of respiratory motion, however, inherently leads to a signal loss of 50% when compared with a conventional J-difference editing technique (JDE). Here, we intend to improve the robustness of a regular JDE (STEAM-ACED) with the use of a BIlinear Rotation Decoupling (BIRD) filter to achieve 100% higher signal gain when compared with ge-HSQC.

Methods: To determine the efficiency of the BIRD filter ^{1}H-[^{13}C] lipid spectra were acquired on 3T from a peanut oil phantom, with three different MR sequences: ge-HSQC, STEAM-ACED, and the BIRD filter together with STEAM-ACED (BIRD-STEAM-ACED). Finally, our proposed method is tested in vivo in five healthy volunteers with varying liver fat content. In these subjects we quantified the ^{1}H-[^{13}C]-signal from the hepatic lipid pool and determined ^{13}C enrichment, which is expected to be 1.1% according to the natural abundance of ^{13}C.

Results: The application of the proposed BIRD filter reduces the subtraction artifact of ^{1}H-[^{12}C] lipid signal efficiently in JDE experiments, which leads to a signal gain of 100% of ^{1}H-[^{13}C]-lipid signals when compared with the ge-HSQC. Phase distortions in vivo were minimal with the use of BIRD compared with STEAM-ACED, which enabled us to robustly quantify the ^{13}C-enrichment in all five subjects.

Conclusion: The BIRD-STEAM-ACED sequence is an efficient and promising tool for ^{13}C-tracking experiments in the human liver in vivo.

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KEYWORDS
^{13}C MRS, ^{13}C tracking, BIRD filter

1 | INTRODUCTION

The application of ^{13}C-MRS together with the administration of specific ^{13}C-labeled substrate enables to measure a large number of metabolic fluxes noninvasively in vivo.[1-3] When compared with direct ^{13}C-MRS, the use of indirect ^{13}C-MRS (i.e., the detection of ^{1}H signals that are coupled to a ^{13}C-nuclei) leads to a large signal gain and allows localization of the MR signal with standard ^{1}H-MRS localization techniques.[4,5] As the natural abundance of ^{13}C is only 1.1%, the efficacy of the spectral editing sequences used is crucial for robust suppression of the large ^{1}H-[^{12}C] signals.

Editing of the ^{1}H-[^{13}C] signal (e.g., indirect ^{13}C) is mainly performed in two different ways; either by regular J-difference editing (JDE) methods or by making use of approaches that allow single-shot acquisitions by applying multiple quantum-coherence (MQC) based sequences.[5] Recently, we demonstrated that it is possible to noninvasively follow the retention of labeled dietary ^{13}C-lipids into the hepatic lipid pool in vivo using gradient enhanced heteronuclear single quantum coherence (ge-HSQC).[6] However, the drawback of applying ge-HSQC is that it inherently leads to a signal loss of 50% when compared with a conventional JDE sequence. Earlier studies have demonstrated the applicability of JDE techniques for ^{13}C tracking applications especially to study glucose metabolism in brain.[7,8] Such JDE techniques are quite challenging to apply directly in liver to track ^{13}C lipids, as respiratory motion will result in imperfect subtraction due to the (large) overlapping ^{1}H-[^{12}C] lipid signal at 1.3 ppm. In a previous study, a JDE sequence was applied on skeletal muscle and liver of rats to study lipid handling;[9] however, it has not been used in humans yet due to the problem of respiratory motion leading to subtraction artifacts. Therefore, the aim of this study was to increase the robustness of a regular JDE technique to increase the edited ^{1}H-[^{13}C] signals when compared with the ge-HSQC methodology, which is required to be able to track the low incorporation rates of ^{13}C lipids in the human hepatic fat pool in vivo.

A STEAM-ACED sequence (STEAM localization with Adiabatic Carbon Editing and Decoupling) has been proposed because of its short TE to minimize the effect of ^{1}H-^{1}H coupling on the acquired signal intensity.[10] A BIRD filter[11] is basically a heteronuclear spin echo with delays equal to 1/2JCH to align ^{1}H spins coupled to ^{12}C and ^{13}C spins in the opposite phase (–*y* and *y* axes), which allows a 90° pulse to align these vectors parallel and antiparallel to the main magnetic field (*z* and –*z* axes) respectively. After a 90° pulse, ^{1}H attached to ^{12}C spins are inverted and will recover based on T_1 relaxation, while ^{1}H attached to ^{13}C spins are along the positive *z*-axis. By choosing an optimal inversion time (TI), it is possible to suppress the ^{1}H-[^{12}C] signal. Here, we hypothesize that pre-suppression of the strong ^{1}H-[^{12}C] lipid signal, by introducing a BIlinear Rotation Decoupling (BIRD) filter prior to a STEAM-ACED sequence, optimized for detection of ^{1}H-[^{13}C]-lipid signals, will lead to an accurate and robust detection of the ^{1}H-[^{13}C] lipid signal irrespective of respiratory motion, with higher signal yield as compared to ge-HSQC.

2 | METHODS

2.1 | General

All MR experiments were performed on a 3T MR system (Achieva 3T-X Philips Healthcare, Best, Netherlands) using a double tuned ^{1}H/^{13}C surface coil (Rapid Biomedical GmbH). The coil was specifically designed for indirect ^{13}C experiments in the liver, with two ^{13}C elements in quadrature arrangement (size of the elements: 13.2 × 21 cm, covering 13.2 × 23.9 cm) and two slightly larger ^{1}H elements in quadrature arrangement (18 × 20 cm and 15 × 15 cm, covering 18 × 20 cm) to achieve optimal sensitivity (Expected at a depth of at least 8-12 cm). All in vivo experiments were performed according to the protocol approved by the Institutional Human Medical Ethics Committee of Maastricht University Medical Centre (MUMC), Maastricht, Netherlands. A written informed consent was obtained from all the subjects prior to participating in this study.

2.2 | MR sequences

For ^{1}H-[^{13}C] editing of the lipid signals, a STEAM-ACED[10] sequence was used with a TE of 7.9 ms (TE1 = TE2 = 3.95 ms = 1/2JCH). Spredrex pulses (Standard Philips 90° excitation pulse) with duration of 2.75 ms were used on the ^{1}H channel for both excitation and selective refocusing of ^{1}H signals. During the TM (Mixing Time) period, an adiabatic inversion pulse with a bandwidth of 1600 Hz was placed on the ^{13}C channel to selectively invert the ^{1}H-[^{13}C] spins. The ^{13}C inversion pulse was used with OFF/ON condition on alternate scans. Subtraction of the acquired data with and without ^{13}C inversion pulse provided MR signals only from ^{1}H attached to ^{13}C nuclei (two times), whereas the sum provided MR signals from all compounds containing ^{1}H but not attached to ^{13}C nuclei (shown in Supporting Information Figure S1, which is available online).

In a next experiment, the BIRD[11] filter was placed prior to the STEAM-ACED sequence. The TI was optimized in vivo to

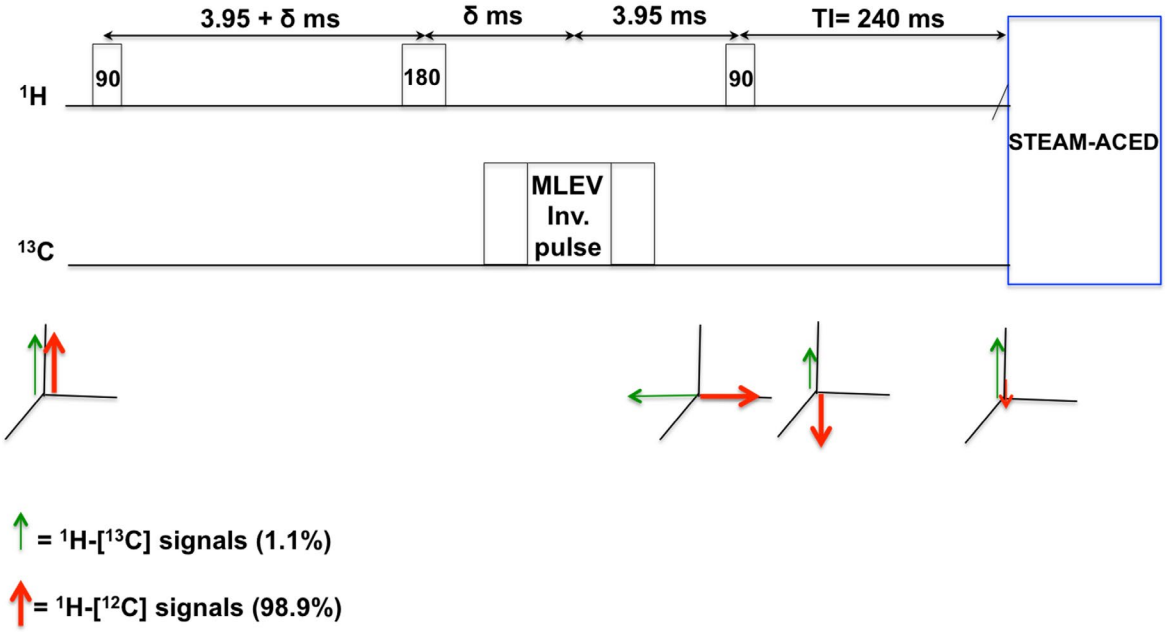

FIGURE 1 Application of a BIRD filter in front of a STEAM-ACED sequence. The filter is basically a spin echo sequence with a ^{13}C inversion pulse (MLEV) added to avoid J-refocusing of the ^{1}H-[^{13}C] signals, which will acquire opposite phase when compared with ^{1}H-[^{12}C] in the *xy*-plane by choosing the appropriate timings. The second 90° pulse is used to flip the ^{1}H-[^{12}C] spins along the –*z*-axis and the ^{1}H-[^{13}C] along the +*z*-axis. The TI is chosen according to the lipid CH_2-T_1 relaxation time in order to null the ^{1}H-[^{12}C] spins. As a result, only ^{1}H-[^{13}C] spins will be excited by the excitation pulse of the localization sequence (STEAM-ACED)

achieve pre-suppression of the large hindering lipid-CH_2 signal (^{1}H-[^{12}C] spins) at 1.3 ppm in order to minimize the subtraction artifact. Block pulses were used in the BIRD filter on the ^{1}H channel for both excitation and selective refocusing of ^{1}H signals. A MLEV inversion pulse was used on the ^{13}C channel as shown in Figure 1, to selectively invert the ^{13}C–CH_2 resonances (Figure 1). In ge-HSQC sequence, the editing was performed with a MQC pulse sequence placed during the TM period.[6]

2.3 | Phantom experiments

All MR sequence parameters and timings were optimized using a peanut oil phantom. Scout MR images were acquired with a turbo spin echo (TSE) sequence with repetition time/echo time (TR/TE) = 2000/100 ms to place a voxel in the center of the phantom. Power calibration was performed using MEGA-sLASER sequence to achieve maximal ^{1}H sensitivity in the volume of interest and the calculated power was kept same for both ^{1}H and ^{13}C channel throughout the experiment. First, STEAM-ACED spectral editing sequence was used to acquire lipid ^{1}H-[^{13}C] MR spectra, once with and without ^{13}C inversion with following parameters TR/TE = 4000/7.9 ms, NSA = 128, voxel = 30 × 30 × 30 mm, data points = 2048. In a second experiment, the BIRD filter was used together with STEAM-ACED to acquire lipid spectra using identical parameters as above, but now with a TI of 240 ms in which the ^{1}H-[^{12}C] lipid signal was maximally suppressed. In a third experiment, ge-HSQC was used as previously described,[6] to acquire ^{1}H-[^{13}C] lipid spectra with a t1 of 4 ms. This set of experiments was used to compare the signal intensity and signal-to-noise ratio (SNR) of ^{1}H-[^{13}C] lipid signal and therefore to determine the efficiency of the BIRD filter. SNR was determined by calculating the ratio of the ^{13}C mean peak height and the standard deviation of noise in the edited spectrum.

2.4 | In vivo MR experiments

Five healthy male subjects (mean age 34 ± 13 years; mean body mass index [BMI] 28.6 ± 3.7 kg/m^2) were included in this study to determine the in vivo feasibility of our proposed approach. The subjects were positioned in the supine position. The ^{1}H/^{13}C surface coil was placed on the right side of the torso to cover the liver region. A fast scout MR image (slice thickness = 15 mm, flip angle = 15°, field of view [FOV] = 450 × 450 × 115 mm) was acquired in three orientations (axial, coronal, and transversal) with four breath holds to verify the positioning of the RF coil in the middle of the liver. A voxel of 45 × 45 × 45 mm was positioned in the liver by avoiding edges of the liver, diaphragm, but also the biliary and vascular structures. STEAM-ACED was used to acquire hepatic lipid ^{1}H-[^{13}C] MR spectra, once with and without ^{13}C inversion with the same MR parameters as used in the phantom. With the same experimental setup, additionally a separate experiment was performed using a BIRD

filter prior to the STEAM-ACED sequence (TI = 240 ms) to selectively pre-suppress the ^{1}H-[^{12}C] lipid signal. The TI = 240 ms was chosen based on the average T_1 relaxation time of lipid-CH_2 in the liver (340 ms), predicting that the signal would be nulled after TI of 240 ms. The long TR (4000 ms) was chosen to allow the subjects to breath in the rhythm of the measurement (MR acquisition at end of expiration) and to avoid saturation effects due to T_1 relaxation.

2.5 | Spectral analysis

All obtained MRS data were post-processed with a custom-built Matlab (version R2017b; The Mathworks Inc.) script. The developed script allowed us to select both series of spectra acquired with and without editing pulses at once for each subject and allowed for automatic phasing, eddy current correction, and frequency alignment of all spectra individually. Moreover, the script automatically removed spectra with poor quality based on a correlation approach, in which all individual spectra were ranked based on the correlation with all other spectra. An equal number of bad quality spectra were removed in both series acquired with and without editing pulse. Finally, the ^{1}H-[^{13}C] lipid resonances obtained in the edited spectrum were fitted as two identical peaks based on iterative based algorithm developed within the Matlab script, using prior knowledge on the known frequency shift of 127 Hz (^{1}H-[^{13}C] coupling for lipid). The best fit for the respective target lipid resonances were selected automatically when there was low residual (difference between fit and actual obtained spectrum) signal.

2.6 | Calculation of ^{13}C natural abundance and hepatic fat %

The total ^{1}H lipid signal coupled to both ^{12}C and ^{13}C spins were determined from the fitted peak of lipid-CH_2 resonance of data acquired only with a conventional STEAM sequence (without ^{13}C inversion pulse in STEAM-ACED). The area of the ^{1}H-[^{13}C] lipid signal (^{13}C natural abundance) was calculated by fitting and adding the two obtained ^{1}H-[^{13}C] lipid-CH_2 resonances in the edited spectrum acquired with and without ^{13}C inversion pulse of STEAM-ACED. The percentage of ^{13}C enrichment was determined using the equation as shown below. Similarly, the ^{13}C lipid signal was also calculated from the data acquired with the BIRD-STEAM-ACED sequence. Then, we compared the calculated percentage of ^{13}C enrichment in both sequences to determine the percentage of signal loss from the expected value of 1.1% (natural abundance). The hepatic fat % was calculated after T_2 correction (water T_2 = 25.1 ms; lipid T_2 = 56.7 ms), using the ratio of $CH_2/(CH_2+H_20)$ from the two spectra obtained with and without water suppression, acquired at TE = 20 ms using conventional STEAM sequence.

$$C^{13}\ \%\text{enrichment} = \left\{ \frac{0.5 \times S\left[C^{13}\right]}{S\,[\text{total}]} \right\} \times 100$$

where $S_{[total]}$ represents the total ^{1}H lipid-CH_2 signal coupled to both ^{12}C and ^{13}C spins (peak at 1.3 ppm in STEAM spectra) and $S_{[C13]}$ indicates only the addition of two signal intensities of ^{1}H-[^{13}C] lipid resonances obtained in the edited spectrum.

3 | RESULTS

3.1 | Phantom

The lipid spectra acquired from the peanut oil phantom using the three different MR sequences are depicted in Figure 2. As expected, the subtraction artifact of ^{1}H-[^{12}C] lipid signal was largely reduced with the ge-HSQC sequence when compared with a regular JDE sequence (STEAM-ACED; Figure 2A,B). Moreover, as expected, the measured ^{13}C% enrichment with

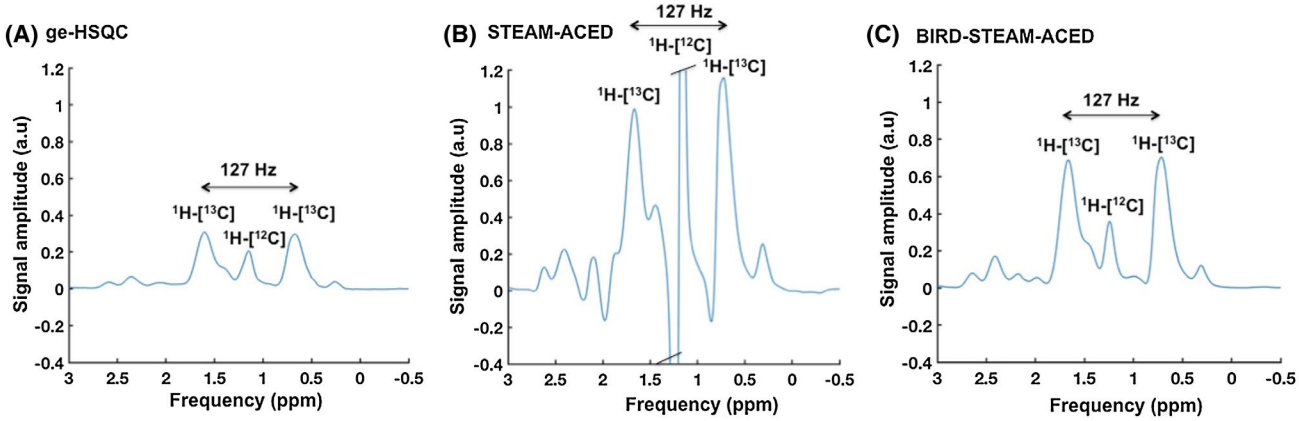

FIGURE 2 ^{1}H-[^{13}C] lipid spectra obtained from the peanut oil phantom with three different sequences. A, ge-HSQC. B, STEAM-ACED. C, BIRD filter together with STEAM-ACED

STEAM-ACED was found to be 0.94% in an oil phantom, indicating only 15% signal loss, as the obtained value is close to the known value of 1.1% (^{13}C natural abundance).

Interestingly, the proposed sequence with the addition of the BIRD filter reduces the subtraction artifact of the ^{1}H-[^{12}C] lipid signal in the oil phantom when compared with a conventional STEAM-ACED sequence. Moreover, the obtained ^{1}H-[^{13}C] lipid signal intensity with the use of the BIRD filter was approximately two-fold higher SNR (173 vs 91) compared with the previously proposed ge-HSQC method (Figure 2C). The measured ^{13}C natural abundance with the BIRD-STEAM-ACED sequence in an oil phantom was found to be 0.74%, indicating 21% signal loss in 1H-[^{13}C] lipid signal intensity due to the BIRD filter compared with the STEAM-ACED sequence alone or if SNR is considered, we find a 16% loss in SNR (206 vs 173).

3.2 | In vivo

Our new method was successfully applied in vivo and demonstrated the feasibility to detect ^{13}C natural abundance in subjects with wide range of liver fat content (2-21%, Table 1). As expected, a large subtraction artifact was apparent in in vivo when a conventional STEAM-ACED sequence was used (Figure 3B). This artifact leads to phase distortions in the edited spectrum, which hampers the accurate and robust quantification of the ^{1}H-[^{13}C] lipid signal (Figure 3B). The addition of the BIRD-filter leads to pre-suppression of the huge ^{1}H-[^{12}C]-lipid signal during MR acquisition and, thereby, leads to marked reduction in the subtraction artifact of the ^{1}H-[^{12}C] lipid signal (Figure 3C).

Due to the implementation of the BIRD filter, we were able to visualize our target ^{1}H-[^{13}C] lipid signal clearly as two distinct peaks with known coupling constant of 127 Hz. We were able to quantify the ^{1}H-[^{13}C] lipid signal successfully in all five subjects. The SNR was sufficient, even in the subject with very low hepatic lipid content. Interestingly, the phase distortions in vivo were minimal with the use of the BIRD filter when compared with STEAM-ACED (Figure 3B,C). The measured ^{1}H-[^{13}C] lipid signal in all five subjects with the use of the BIRD-STEAM-ACED sequence are shown in the Table 1.

TABLE 1 Measured ^{1}H-[^{13}C] lipid signal (natural abundance) with the BIRD-STEAM-ACED sequence in five different subjects with varying hepatic fat content (%)

	Fat %	^{13}C%-BIRD-STEAM-ACED
Subject 1	13.8	0.58
Subject 2	3.5	0.63
Subject 3	3.3	0.54
Subject 4	20.6	0.53
Subject 5	2.4	0.63
Mean		0.58 ± 0.05

4 | DISCUSSION

In this study, we improved the robustness of a regular JDE (STEAM-ACED sequence) technique for the application in human liver with the use of the BIRD filter and demonstrated the in vivo feasibility of our proposed approach. We were successful in the determination of the ^{13}C (natural abundance) lipids in hepatic fat pool in all five subjects. The subtraction artifact of the ^{1}H-[^{12}C] lipid signal is efficiently reduced with the use of the BIRD filter compared with the conventional STEAM-ACED. Therefore, the two distinct peaks of the ^{1}H-[^{13}C] lipid-CH_2 signal were clearly visible with the use of the BIRD filter together with STEAM-ACED spectral editing sequence. Interestingly, with the BIRD filter, there is a minimum signal loss in ^{13}C lipid signal intensity in phantom compared with the conventional STEAM-ACED.

The addition of the BIRD filter leads to inherent ^{1}H-[^{13}C] signal loss, probably due to ^{1}H-^{1}H couplings. However, due to T_1 recovery, the ^{1}H-[^{13}C] signal losses due to the BIRD filter will be less with longer TI (when TI > actual null TI of lipid-CH_2), which results in higher ^{1}H-[^{13}C] signal intensity. We aimed at nulling the ^{1}H-[^{12}C] signal with the chosen TI. A longer TI would provide higher ^{1}H-[^{13}C] lipid signal intensity, but simultaneously the ^{1}H-[^{12}C] residue will also be increased. Thus, there is a tradeoff between ^{12}C and ^{13}C lipid signals. Due to differences in T_1 relaxation time between in vivo and the oil phantom (340 vs 270 ms), the degree of recovery is slightly different; therefore, the oil phantom provides higher enrichment (0.74%) than in vivo (0.58%) while using identical TI (shown in Supporting Information Figure S2).

Moreover, both phantom and in vivo measurements yield lower ^{13}C enrichment than expected (^{13}C natural abundance of 1.1%). This indicates that there is (systemic) inherent signal loss, which might be due to ^{1}H-^{1}H couplings. However, this is not a problem for ^{13}C tracking applications in liver when indirect ^{13}C MRS is generally used to measure changes in the ^{13}C% enrichment, as the baseline enrichment can be set to 1.1%. This inherent signal loss will be taken into account to calculate the absolute ^{13}C% enrichment.

Interestingly, the in vivo measured ^{13}C lipid signal enrichment (natural abundance) with the BIRD-STEAM-ACED sequence was very similar among all subjects with varying liver fat content, suggesting that the present approach is very robust. Due to the insertion of the B1-insensitive MLEV pulse on the ^{13}C channel in the BIRD filter, signal loss is minimized, irrespective of B1 inhomogeneity while using a surface coil. In contrast, some B1 inhomogeneity is expected due to the use of standard pulses on the ^{1}H channel, and while this can lead to some signal loss in absolute terms, it will not affect the estimation of ^{13}C enrichment, as both the ^{1}H-[^{13}C] signal and the reference signal are equally affected. Due to phase distortions and a large residual of ^{12}C artifact,

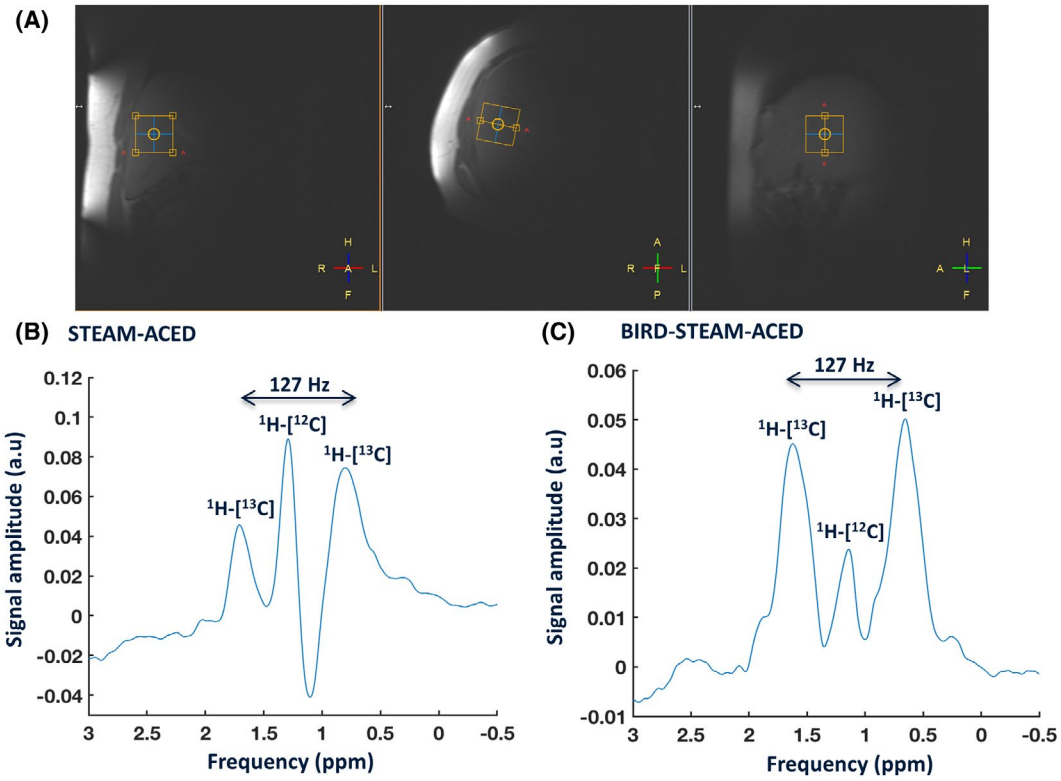

FIGURE 3 A, Screenshot of scout MR image showing the voxel position in three different orientations of a volunteer. ^{1}H-[^{13}C] hepatic lipid spectra obtained from the voxel with two different MR sequences. B, STEAM-ACED. C, BIRD filter together with STEAM-ACED

approaches to quantify the ^{1}H-[^{13}C] lipid signal intensity with solely STEAM-ACED were not successful in vivo. Thus, our proposed sequence with the BIRD filter was designed to minimize ^{1}H-[^{12}C] signal and was successfully applied in vivo in subjects with varying total liver fat content and showed higher SNR for ^{13}C lipids (natural abundance), even in the subject with low liver fat content.

Also the ge-HSQC provides excellent editing of the ^{1}H-[^{13}C] lipid-CH_2 peak in an oil phantom, but the signal loss of >50% compared with a conventional STEAM-ACED is unavoidable. Our proposed sequence with the BIRD filter leads to a large signal gain in ^{1}H-[^{13}C]-lipid signal intensity and SNR (almost two-fold) when compared with ge-HSQC. Next to this, the use of JDE in combination with BIRD also has other advantages when compared with ge-HSQC. Due to the relatively long T_1, the hepatic water signal intensity is not much affected by the optimized TI of 240 ms. Therefore, the residual water signal can be used to perform phase and frequency alignment of individual spectra, whereas in ge-HSQC, this is not possible due to the gradient de-phasing of all ^{1}H-[^{12}C] lipid signals and also water signals.[6] Also, a signal gain is expected when compared with ge-HSQC in practice due to the insertion of B1 insensitive pulses in our approach (MLEV pulse in the BIRD filter and adiabatic hyperbolic secant pulse in the TM period of the STEAM-ACED sequence). In contrast to ge-HSQC, miscalibration of the ^{13}C transmit power does not per se lead to lower a ^{13}C-enrichment, due to the B1 insensitivity of the pulses used in the proposed approach. The higher ^{13}C signal (compared with ge-HSQC) together with minimal ^{12}C artifact with the use of the BIRD filter will enable to track even the smaller contribution of labeled glucose[12] to form ^{13}C lipids (compared with the contribution from ^{13}C-labeled fatty acids) in the hepatic fat pool. Thus, our proposed approach can now be used as an efficient and promising tool for ^{13}C tracking applications in vivo.

5 | CONCLUSION

The proposed sequence with the BIRD filter reduces the subtraction artifacts of ^{1}H-[^{12}C] lipid signal efficiently without much signal loss in the target ^{1}H-[^{13}C] lipid signal; thus, it can be used as an indirect ^{13}C method for ^{13}C tracking applications in liver.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Pandichelvam Veeraiah https://orcid.org/0000-0002-9149-7483

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

FIGURE S1 Sequence diagram of STEAM-ACED sequence.[10] An adiabatic inversion pulse with bandwidth of 1600 Hz is only applied on ^{13}C channel on alternate scans for editing purpose

FIGURE S2 ^{1}H-MR lipid spectra acquired with different TI values from the peanut oil phantom (A) and from a healthy volunteer (B) using an inversion recovery with STEAM sequence. Plotted the signal intensity of lipid-CH_2 vs TI in the respective figure. The null TI (indicated by arrow) for the lipid-CH_2 was found to be 186 ms and 240 ms in oil phantom and in vivo respectively. Therefore T_1 of lipid-CH_2 was estimated to be 270 ms in this oil phantom and 340 ms in in vivo

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