Reproducibility of two-point DIXON technique for measuring hepatic fat fraction

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Hepatic steatosis is characterized by an increased deposition of triglycerides within the cytoplasm of hepatocytes, and may subsequently lead to steatohepatitis, fibrosis and irreversible cirrhosis. Quantification of hepatic fat could facilitate early interventions and treatments of fatty liver, thus reducing its associated risks.

Percutaneous liver biopsy has been considered the gold standard for assessment of hepatic steatosis. However, liver biopsy is invasive in nature with potential complications and its ability to assess disease progression and treatment response longitudinally is limited by the sampling error and interobserver variations.

Proton magnetic resonance spectroscopy (1H MRS) allows the study of cellular biochemistry and metabolism, determining disease abnormalities and progression in vivo and longitudinally. Recently, 1H MRS has been considered a sensitive and non-invasive tool to detect hepatic steatosis by measuring hepatic fat fraction (HFF), which highly correlates with liver biopsy results. However, this single voxel technique is problematic due to heterogeneity of steatosis and requires extensive post-processing analysis.

Two-point DIXON (2PD), a water-fat separation MR technique using chemical shift principle, provides an alternative means for measurements of HFF non-invasively. 2PD with gradient echo sequence has been increasingly used in quantifying HFF with in-phase (IP) and out-of-phase (OP) images, demonstrating correlations with 1H MRS or liver biopsy results. Hepatic steatosis could be diagnosed with high sensitivity and specificity using 2PD.

Detection of alterations associated with pathology, disease progression or therapeutic intervention depends on reproducibility of the technique; therefore, determination of precision of the measurements is important for patient management towards diagnosis, treatment and follow-up. Reproducibility of 1H MRS has been reported in both normal and diseased populations; however, reproducibility study of 2PD has been limited so far. In this study, we aim to evaluate reproducibility of 2PD for measuring HFF in healthy subjects, and compare with that of 1H MRS.
Methods and Materials

Study Population: This study was conducted with the approval of the institutional review board and with informed consent. 15 healthy subjects were included in this study (9 males and 6 females; age = 30.5 ± 8.2 years; body mass index (BMI) = 25.3 ± 3.0 kg/m\(^2\)). 7 subject were overweight (25 kg/m\(^2\) # BMI < 30kg/m\(^2\)) and 1 subject was obese (BMI # 30 kg/m\(^2\)). None of the subjects had diabetes, history of liver disease, or excessive alcohol consumption.

MRI: All MRI examinations were performed on a 1.5 T Siemens MRI scanner (MAGNETOM Tim Aera; Siemens Medical Solutions, Erlangen, Germany), with the subject lying in a supine position. Scout images were first acquired in three orthogonal planes with a two-dimensional (2D) fast low-angle shot (FLASH) sequence. The 2PD and \(^1\)H MRS data were acquired from all subjects.

For breath-holding, subjects were instructed to inhale, exhale; then inhale and hold their breath at deep inspiration. Duplicate measurements were acquired in each subject after repositioning. Note that care was taken to maintain similar slices and voxel localization for 2PD and \(^1\)H MRS, respectively. Single breath-hold 2PD was performed axially using a three-dimensional (3D) FLASH sequence with repetition time (TR) = 7 ms, echo time (TE) = 2.38 and 4.76 ms (OP and IP, respectively), flip angle (FA) = 10º, field of view (FOV) = 35 × 35 × 19.2 cm\(^2\), acquisition matrix = 256 × 256 × 64, spatial resolution = 1.37 × 1.37 × 3 mm\(^3\), number of excitations (NEX) = 1 and total scan time of 17 sec. HFF maps were calculated on a pixel-by-pixel basis as follows: HFF = [(S\(_\text{in}\) - S\(_\text{out}\)) / (2 × S\(_\text{in}\)) × 100%]\(^{18,33}\), where S\(_\text{in}\) and S\(_\text{out}\) are signal intensities of IP and OP images respectively.

A circular ROI of 4 cm\(^2\), with location corresponded to those used for \(^1\)H MRS acquisition, was defined to encompass a large homogeneous liver region in the right hepatic lobe containing no large blood vessels for HFF measurements. For \(^1\)H MRS, a 2 × 2 × 2 cm\(^3\) voxel was placed over a homogeneous liver parenchyma in the right hepatic lobe with care taken to avoid large blood vessels. After automatic adjustments of shim terms for localized voxel, a full-width half-maximum linewidth of water signal of # 50 Hz would be achieved. Single breath-hold stimulated echo acquisition mode (STEAM) sequence without water suppression was used for signal acquisition using TR = 2000 ms, TE = 20 ms, spectral bandwidth = 1.2 kHz, 1024 data points, 4 averages and total scan time of 16 sec. The in vivo MR spectra were processed using the jMRUI software\(^{34}\). Metabolite areas of water (at 4.7 ppm) and lipid (at 1.3 ppm) were estimated using the quantitation
based on advanced methods for accurate, robust, and efficient spectral fitting (AMARES) algorithm\textsuperscript{35}. After correction for \(T_2\) relaxation (\(T_{2\text{water}} = 34\) ms, \(T_{2\text{fat}} = 68\) ms)\textsuperscript{36}, HFF was then calculated as \(\frac{\text{Area}_{\text{lipid}}}{(\text{Area}_{\text{water}} + \text{Area}_{\text{lipid}})} \times 100\%\)\textsuperscript{18,32,37}.

**Data and Statistical Analysis:** Relationships between HFF measurements from 2PD and \(^1\)H MRS were evaluated by calculating Spearman's correlation coefficient. Reproducibility of the measurements was assessed using Bland-Altman method\textsuperscript{38}. Coefficient of variation (CV), repeatability coefficient (RC) and intraclass correlation coefficient (ICC) were also computed. CV was estimated as the within-subject standard deviation (#\(_{ws}\)) divided by the mean, measuring the precision of the measurement\textsuperscript{38,39}. RC was defined as \(1.95 \times \#2 \times \#_{ws}\), and indicates the possible minimum detectable biologic differences\textsuperscript{28,38,39}. ICC considers both within-subject variances arising from measurement error and between-subjects variance as \(\text{ICC} = \frac{\#_{bs}^2}{\#_{bs}^2 + \#_{ws}^2}\), where #\(_{bs}\) denotes between-subjects standard deviation. ICC determines the fraction of the total variance that was attributed to true biologic variation instead of measurement error\textsuperscript{28,40}. Note that the reproducibility parameters (CV, RC and ICC) include variations resulting from repositioning and real biologic changes between 2 imaging sessions. Two-tailed Wilcoxon matched pairs tests were performed between 2PD and \(^1\)H MRS for reproducibility parameters, with \(p < 0.05\) considered as statistically significant.
Results

Fig. 1 shows representative IP, OP, calculated HFF images using 2PD and 1H MRS spectra from the same subject. All 2PD and 1H MRS measurements were of adequate quality for analysis in all subjects. All subjects were able to cooperate for the breath holding at deep inspiration, and no examinations had to be repeated.

Fig. 2 shows the HFF measurements from 2PD and 1H MRS for all the subjects studied. HFF measured using 2PD and 1H MRS for all subjects were 5.56 ± 7.09% and 4.86 ± 6.62% respectively. A strong correlation between the HFF measurements was observed (r = 0.92; p < 0.001).

Fig. 3 depicts the Bland-Altman plots for 2PD and 1H MRS. For 2PD, the mean difference between the two measurements was 2.1%, with limits of agreement between -16.5% and 20.8%. In contrast, the mean difference between the two measurements for 1H MRS was 2.6%, with limits of agreement between -70.2% and 75.3%.

The CV, RC and ICC values of the HFF measurements from 2PD and 1H MRS were summarized in Table 1. Significant decrease (p < 0.01) in CV was found for 2PD (5.2 ± 4.3%), as compared with that for 1H MRS (19.1 ± 17.4%). Similarly, RC for 2PD (0.39 ± 0.37%HFF) was significantly lower (p < 0.01) than that for 1H MRS (1.55 ± 2.56%HFF). Moreover, ICC for 2PD (1.00 ± 0.00) was found to be significantly higher (p < 0.01) than that for 1H MRS (0.98 ± 0.06). The reproducibility parameters of 1H MRS in this study were comparable to that reported previously30, 31,41. Bland-Altman plots allow investigation the variation in repeated measurements, while 95% of differences in repeated measurements are expected to lie within the limits of agreement38.

In Fig. 3, it is obvious that 2PD demonstrated smaller limits of agreement, suggesting that repeated measurement variation using 2PD is smaller. CV describes the precision of a technique38, 39. CV for 2PD was significant decreased compared with that for 1H MRS, suggesting the higher precision value of 2PD in measuring HFF. Besides, the possible minimum detectable biologic differences, RC, of 2PD were significantly lower than that of 1H MRS. Moreover, ICC, the fraction of the total variance that was attributed to true biologic variation instead of measurement error, for 2PD were significantly higher than that for 1H MRS. These results indicates that 2PD shows a lower interscan variability for longitudinal studies in quantifying HFF.
Fig. 1: Representative in-phase (IP), out-of-phase (OP), calculated hepatic fat fraction (HFF) images using two-point DIXON (2PD) and proton magnetic resonance spectroscopy (1H MRS) spectra from the same subject.

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Fig. 2: In vivo HFF measurements using 2PD and 1H MRS for all subjects. A strong correlation between the HFF measurements was observed \((r = 0.92; p < 0.001)\).

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Fig. 3: Bland-Altman plots of 2PD and 1H MRS in measuring HFF for all subjects. For 2PD, the mean difference between the two measurements was 2.1%, with limits of agreement between -16.5% and 20.8%. In contrast, the mean difference between the two measurements for 1H MRS was 2.6%, with limits of agreement between -70.2% and 75.3%.

Table 1: Coefficient of variation (CV), repeatability coefficient (RC) and intraclass correlation coefficient (ICC) using two-point DIXON (2PD) and proton magnetic resonance spectroscopy (1H MRS) in measuring hepatic fat fraction (HFF) of all subjects. All data were presented as mean ± standard deviation (SD). Two-tailed Wilcoxon matched pairs tests were employed between 2PD and 1H MRS for reproducibility parameters, with p < 0.05 considered as statistically significant.
Conclusion

In conclusion, the experimental results demonstrated that 2PD exhibited higher reproducibility than $^1$H MRS in measuring HFF non-invasively. Significant decrease in CV, RC and significant increase in ICC were observed with 2PD measurements, comparing with $^1$H MRS. Without extensive post-processing analysis, 2PD may offer promise as a robust non-invasive tool to measure HFF for the entire liver reproducibly in diagnosis, treatment and follow-up of hepatic steatosis at clinical field strength within a single breath-hold.
References
