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Myocardial triglycerides : magnetic resonance spectroscopy in health and diabetes

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Chapter 2

Metabolic Imaging of Myocardial Triglyceride Content: Reproducibility of ^1H MR Spectroscopy with Respiratory Navigator Gating in Volunteers

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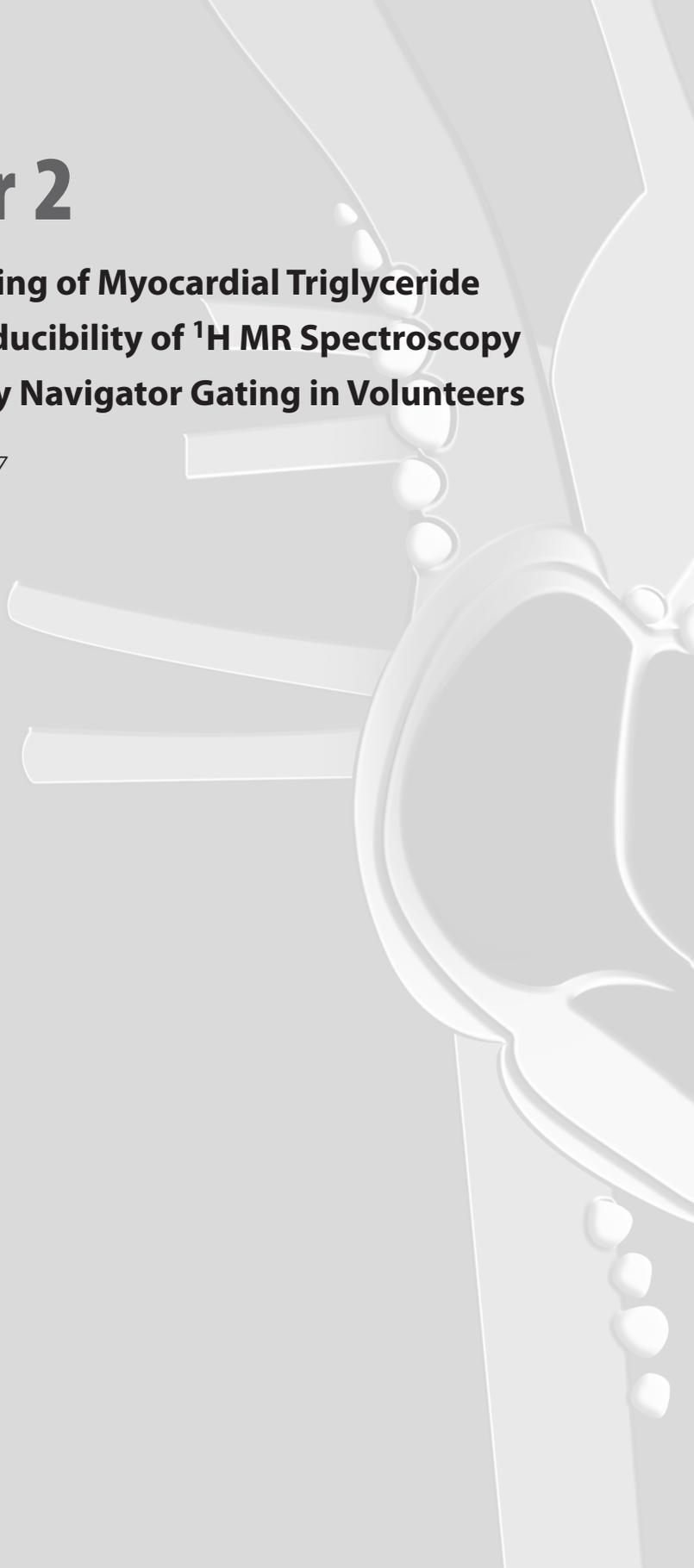
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SUMMARY

Objectives: The purpose of the study was to prospectively compare spectral resolution and reproducibility of ^1H magnetic resonance spectroscopy ($^1\text{HMRS}$), with and without respiratory motion compensation based on navigator echoes, in the assessment of myocardial triglyceride (TG) content in the human heart.

Materials and methods: In 20 volunteers (14 men, 6 women; mean age \pm standard error, 31 ± 2.8 years [range, 19-60 years]; body mass index, 19-30 kg/m 2) without history of cardiovascular disease, $^1\text{HMRS}$ of the myocardium was performed at rest, with and without respiratory motion compensation.

Results: Unsuppressed water signal linewidth changed from 11.9 Hz to 10.7 Hz ($P < 0.001$) with the use of the navigator, which indicated better spectral resolution. The navigator improved the intraclass correlation coefficient for the assessment of myocardial TG content from 0.32 to 0.81.

Conclusions: It is concluded that respiratory motion correction is essential for reproducible assessment of myocardial TGs.

INTRODUCTION

Hydrogen 1 magnetic resonance (MR) spectroscopy (¹HMRS) is a promising tool for metabolic imaging to assess triglyceride (TG) content of myocardial tissue in humans (1-3). Findings from rat studies have shown that there is a negative correlation between myocardial TG content and heart function, while treatment with insulin-sensitizing drugs reduced myocardial TG deposition and reversed contractile dysfunction in lipotoxic heart disease in obese Zucker rats (4-6). These findings suggest that intramyocardial TG accumulation is deleterious to the heart (7). Furthermore, myocardial TG content may be a marker of myocardial viability after coronary occlusion due to enhanced esterification and/or reduced oxidation of fatty acids in ischemically insulted but viable myocardium (8).

Motion artifacts from cardiac and respiratory motion have a negative effect on the reliability of myocardial ¹HMRS. Motion of the heart relative to the volume of interest may lead to reduced spectral resolution and contamination of the ¹HMR spectrum by, for example, epicardial fat. In addition, respiratory motion may negatively influence ¹HMR spectral resolution by preventing optimal shimming and water suppression. Several methods for respiratory gating have been proposed to improve repeatability and spectral resolution at ¹HMRS (2;3;9). Recently, respiratory navigator gating and volume tracking for double-triggered cardiac ¹HMRS became available (10). However, the influence of respiratory navigator gating on spectral resolution and on the reproducibility of myocardial TG measurements is unknown. Therefore, the purpose of our study was to prospectively compare spectral resolution and reproducibility of ¹HMRS, with and without respiratory motion compensation based on navigator echoes, to assess myocardial TGs in the human heart.

MATERIALS AND METHODS

One of the authors (M.S.) is an employee of Philips Medical Systems (Cleveland, Ohio). This author provided technical and intellectual input to the study. The authors who were not employed by Philips Medical Systems had full control of the inclusion of the data and information that might have presented a conflict of interest for this author. In 20 volunteers (14 men, 6 women; mean age \pm standard error, 31 ± 2.8 years [range, 19-60 years]; body mass index, 19-30 kg/m²) without a history of cardiovascular disease, ¹HMRS of the myocardium was performed at rest. Furthermore, one healthy male subject (age, 22 years; body mass index, 23 kg/m²) underwent ¹HMRS before and after a very low-calorie diet. This healthy subject had no history or clinical evidence of cardiovascular disease, diabetes, or any other chronic disease (screening visit consisted of a medical history, physical examination, electrocardiography [ECG], and screening laboratory tests such as fasting plasma glucose and lipid levels and an oral glucose tolerance test). The

medical ethical committee of our institution (Leiden University Medical Center, Leiden, The Netherlands) approved our study protocol, and all participants gave informed consent.

Study design

ECG-triggered ^1H MRS was performed twice during one session with the same parameters, without changing the position of the voxel, both with and without the use of respiratory navigator gating and volume tracking. Thereafter, the volunteer was removed from the imager. After 5 minutes, the volunteer was repositioned in the magnet bore, and ECG-triggered ^1H MRS was repeated with and without respiratory navigator gating and volume tracking after completing all preparation phases. No marking of coil position on the chest wall of subjects or other efforts to minimize variability were performed. To test the ability of respiratory navigator-gated ^1H MRS to demonstrate changes in myocardial TG content after metabolic interventions, ^1H MRS was performed in one volunteer before and after a 3-day very low-calorie diet. The low-calorie diet consisted of 471 kilocalories, 50.2 g of carbohydrates, and 6.9 g of fat (0.94 g saturated fat, Modifast Intensive; Nutrition & Santé Benelux, Breda, The Netherlands) per day. The volunteer was instructed to remain fasted for 4 hours prior to both ^1H MRS examinations.

Magnetic resonance technique

Cardiac MR examinations were performed at 1.5-Tesla (Gyrosan ACS/NT15; Philips, Best, The Netherlands). A 17-cm diameter circular surface coil, with a vitamin-A capsule in the center for visualization of the coil center on survey images, was positioned on the chest wall. Gradient-echo survey images were acquired to verify location of the ^1H MRS surface coil. When necessary, the coil was repositioned to place the coil center just below the mitral valve level of the heart (Figure 2.1). Once the coil was at the correct position, ECG-triggered MR imaging was performed to acquire multiphase gradient-echo images (repetition time ms/ echo time ms, 3.5/1.75; 35-40 heart phases) in the four-chamber and short-axis views to image the interventricular septum and to determine the time point of end-systole (Figure 2.1).

^1H magnetic resonance spectroscopy technique

ECG-triggered cardiac ^1H MRS spectra were obtained from the interventricular septum with subjects in the supine position. The body coil was used for radiofrequency transmission, and the 17-cm diameter circular surface coil was used for signal reception. An 8-ml voxel ($4 \times 2 \times 1$ cm) was positioned in the interventricular septum on the four-chamber and short-axis images at end-systole, thereby avoiding contamination from epicardial fat (Figure 2.1). A section-selective 90° pulse, followed by two section-selective refocusing pulses (a pointresolved spectroscopy sequence) was used to acquire single-voxel MR spectroscopic data (1). Spectra were acquired at end-systole, with an echo time of 26 ms and a repetition time of at least 3000 ms; 1024 data points were collected by using 1000-Hz spectral width and 128 signals acquired. The repetition time of 3000 ms was chosen to approach complete relaxation of the TG signals. A pencil

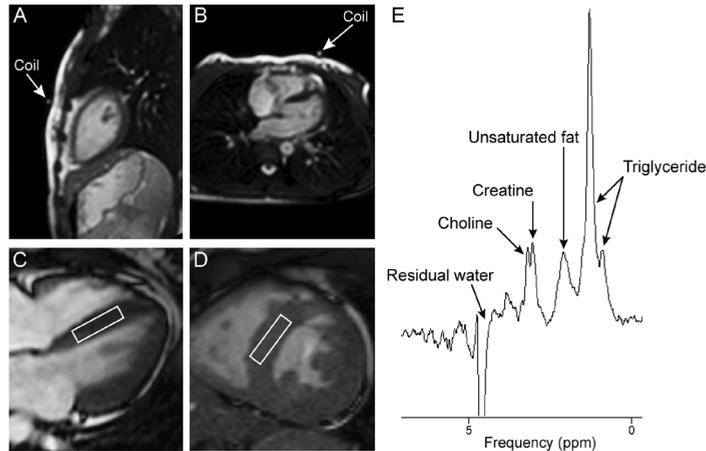


Figure 2.1.

Images show coil position and spectroscopic volume. The surface coil was positioned just below the mitral valve level of the heart on, A, sagittal and, B, transverse balanced steady-state free precession magnetic resonance (MR) images. Spectroscopic volume localization in the interventricular septum on, C, four-chamber and, D, short-axis views (ECG-triggered balanced steady-state free precession MR is demonstrated). Care was taken to avoid contamination from epicardial fat. E, Typical water-suppressed ¹H spectrum of myocardial tissue located in the interventricular septum (128 signals acquired; voxel size 8 ml). Peak heights are in arbitrary units, ppm = parts per million.

beam navigator was positioned on the lung-liver interface of the right hemidiaphragm (Figure 2.2) for respiratory motion gating and tracking (10-12) by one of the authors (R.W.v.d.M.). A two-dimensional spatially-selective radiofrequency pulse for pencil beam-shaped excitation was used. A pencil beam with a diameter of 25 mm and a length of 80 mm was selected. Respiratory navigator-gated spectroscopic data were accepted during data acquisition when the diaphragm-lung interface was within a predefined acceptance window of 5 mm around end expiration.

Motion tracking was used to compensate for any residual translational shifts of the diaphragm-lung interface within the predefined acceptance window. The assumed scale factor between diaphragmatic motion and cardiac motion in the feet-to-head direction was 0.6 (13). Automatic center frequency determination, gradient shimming, transmit power, receiver gain optimization, and water suppression were performed by using respiratory navigator gating and tracking. Without changing any parameter, a spectrum without water suppression was obtained, with a repetition time of 10000 ms (to approach complete relaxation of the water signal) and four signals acquired, to be used as an internal reference (see next section). Total acquisition time for both a watersuppressed and a water-unsuppressed spectrum, including (re-)positioning of the patient, shimming, and parameter adjustment for water suppression, was on average 25 minutes. Assessment of a single, water-suppressed spectrum with 128 signals acquired took approximately 10 minutes depending on the respiratory cycle of the volunteer and on the acceptance rate of the respiratory navigator.

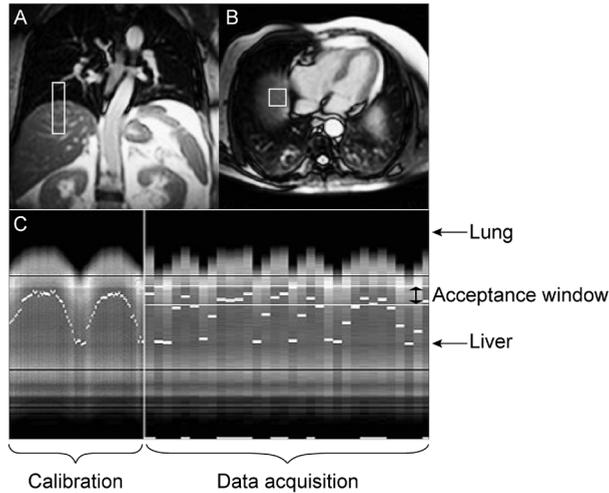


Figure 2.2.

Images show position of pencil beam on right hemidiaphragm. A, Coronal and B, transverse balanced steady-state free precession magnetic resonance images show positioning of pencil beam on right hemidiaphragm. C, White dots (left) represent the automatically traced position of diaphragm (pencil beam excitation pulse is applied in foot-head direction). Two respiratory cycles are used for calibrations (smooth white line); thereafter, during data acquisition, navigator samples are taken with lower temporal resolution (white points, right). White horizontal lines indicate acceptance window (end-expiration, 5 mm); whenever the detected motion state of the diaphragm is within the window, the spectroscopic measurement is accepted.

Spectral quantification

All ^1H MRS data were fitted in the time domain, directly on free induction decays by using Java-based MR user-interface software (jMRUI version 2.2; A. van den Boogaart, Katholieke Universiteit Leuven, Leuven, Belgium) (14) in consensus by two authors (R.W.v.d.M. and H.J.L., with 2 and 15 years of experience in myocardial MR imaging, respectively). The Hankel-Lanczos filter (single-variable decomposition method) was used to remove residual water signal from spectra acquired with water suppression. Myocardial TG signal amplitudes were analyzed automatically by using the Advanced Magnetic Resonance, or AMARES, fitting algorithm within the jMRUI software (15). The AMARES fitting algorithm within jMRUI also provides the standard deviation of the amplitude (one time the Cramer-Rao standard deviation [CRSD]), which can be used as a measure of the accuracy of the fitted signal amplitude, reflecting the signal-to-noise ratio (16). The CRSD of the lipid signal was divided by the lipid signal amplitude, yielding a relative CRSD, which is inversely related to the signal-to-noise ratio. Resonance frequency estimates for intramyocardial lipids were described with the assumption of Gaussian line shapes at 0.9, 1.3, and 2.1 parts per million (ppm). (In keeping with the approach of Torriani *et al.* (17), we summed the amplitudes of lipid resonances at 0.9 and 1.3 ppm for TG quantification for statistical analysis). Prior knowledge was incorporated into the fitting algorithm by using previously published criteria (18-20). Fixed frequencies for TG peaks were used, and linewidths and amplitudes were

unconstrained. The zero-order phase correction was estimated by using the AMARES algorithm, and the first-order phase correction was fixed to 0.13 ms. The water signal from spectra without water suppression obtained from the same voxel was used as internal reference for relative quantification of lipid resonances. The water signal peak at 4.7 ppm was quantified and the linewidth (full width at half maximum) was calculated by using a Lorentzian line shape in the AMARES algorithm. The percentage of myocardial TG content relative to water was calculated as the signal amplitude of TGs divided by the signal amplitude of water, and multiplied by 100.

Statistical analysis

To compare reproducibility of percentage of myocardial TG content with and without respiratory navigator gating and volume tracking, the intraclass correlation coefficients were calculated by using a mixed-effects analysis of variance (with patients as random factor) for both conditions separately. Furthermore, the coefficients of variance were calculated for both conditions separately. Moreover, Bland-Altman plots were constructed. Statistical significance of differences was assessed by using two-tailed paired t-tests, and $P < 0.05$ was considered to indicate a significant difference. Mean values \pm standard errors are given. Statistical analyses were performed by using statistical software (SPSS, version 12.01; SPSS, Chicago, Ill).

RESULTS

The full width at half maximum value of the unsuppressed water signal changed from $11.9 \text{ Hz} \pm 0.4$ to $10.7 \text{ Hz} \pm 0.44$ (all data pooled, $P < 0.001$), without and with respiratory navigator gating, respectively. A decrease was observed in the calculated mean myocardial TG percentage with use of respiratory navigator gating compared with myocardial TG percentage assessed without use of the navigator (Table 2.1).

In all acquisition conditions, the CRSD was less than 1% of the lipids signal amplitude.

Bland-Altman plots of the observed percentage of myocardial TGs without and with respiratory navigator showed smaller limits of agreement (mean \pm 2 standard deviations) when respiratory navigator is used, indicating improved reproducibility (Figure 2.3). Without use of

Table 2.1. Reproducibility of human myocardial triglyceride content.

Data	Without navigator		With navigator	
	%TG*	Relative CRSD (%) [†]	%TG*	Relative CRSD (%) [†]
All data (n=40)	0.46 ± 0.02	0.80 ± 0.07	$0.38 \pm 0.02^{\ddagger}$	0.92 ± 0.09
Acquisition 1 (n=20)	0.43 ± 0.03	0.86 ± 0.12	$0.37 \pm 0.03^{\ddagger}$	0.95 ± 0.12
Acquisition 2 (n=20)	0.48 ± 0.03	0.74 ± 0.09	$0.40 \pm 0.03^{\ddagger}$	0.89 ± 0.12

Data are mean \pm standard error. * Relative to the water signal.

[†] CRSD (cramer-rao standard deviation) relative to the triglyceride (TG) signal amplitude. Relative CRSD was used as a representative for the signal-to-noise ratio. [‡] Percentage of TGs without navigator is significantly different from that with navigator (two-tailed paired t-tests, $P < 0.05$).

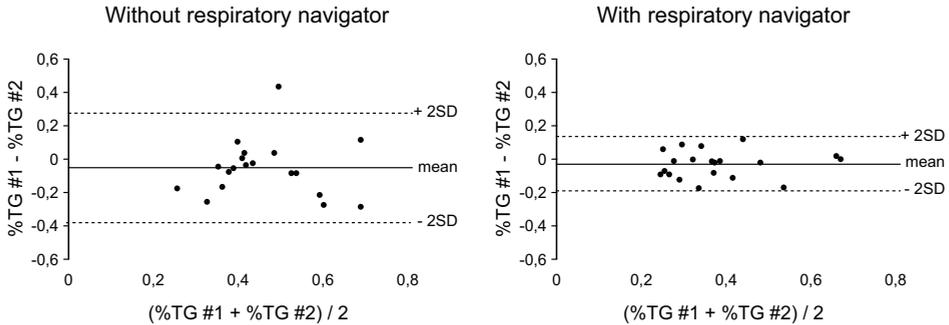


Figure 2.3

Bland-Altman plot of metabolic imaging of myocardial triglyceride (TG) content without (left) and with (right) respiratory navigator gating and volume tracking. Without respiratory navigator gating, the mean interacquisition difference (\pm standard error) of the percentage of TGs is $-0.05\% \pm 0.04$ ($P = 0.20$); with respiratory navigator gating, the difference of the two acquisitions in the same subjects is $-0.03\% \pm 0.02$ ($P = 0.11$). No trends are observed. Limits of agreement (mean \pm 2 standard deviations [2SD]) are smaller when respiratory navigator is used, indicating improved reproducibility.

%TG = myocardial TG percentage relative to unsuppressed water, #1 and #2 = acquisitions 1 and 2.

the respiratory navigator, the intraclass correlation coefficient was 0.32 (95% confidence interval: $-0.14, 0.66$; $P = 0.08$), and this coefficient improved to 0.81 (95% confidence interval: $0.58, 0.92$; $P < 0.001$) with use of navigator gating and volume tracking. Furthermore, the coefficient of variation of the assessment of myocardial TG percentage without use of the navigator was 14.5% higher than with the use of the navigator (32.4% vs 17.9%). The very low-calorie diet induced an 83% increase in myocardial TG content compared with baseline percentage of TGs (1.1% and 0.6 %TG content, respectively) (Figure 2.4) in one volunteer.

DISCUSSION

In our study, reproducibility of metabolic imaging findings by using ECG-triggered ^1H MRS to assess myocardial TG accumulation was assessed with and without the use of respiratory navigator echo-based motion compensation. Spectral resolution (defined by means of the linewidth of the unsuppressed water signal), which is a measure of spectroscopic quality, increased significantly ($P < 0.001$) with use of respiratory motion compensation. Furthermore, reproducibility of the assessment of myocardial TG content was improved when respiratory navigator gating was applied.

Respiratory motion causes a relative displacement of the acquisition volume in relation to the position of the human heart. Thereby, respiratory motion may hamper shimming and water suppression. In our study, the full width at half maximum values of the unsuppressed water signal decreased significantly with use of the respiratory navigator compared with acquisitions without respiratory navigator gating and tracking. The observed values in our study of full

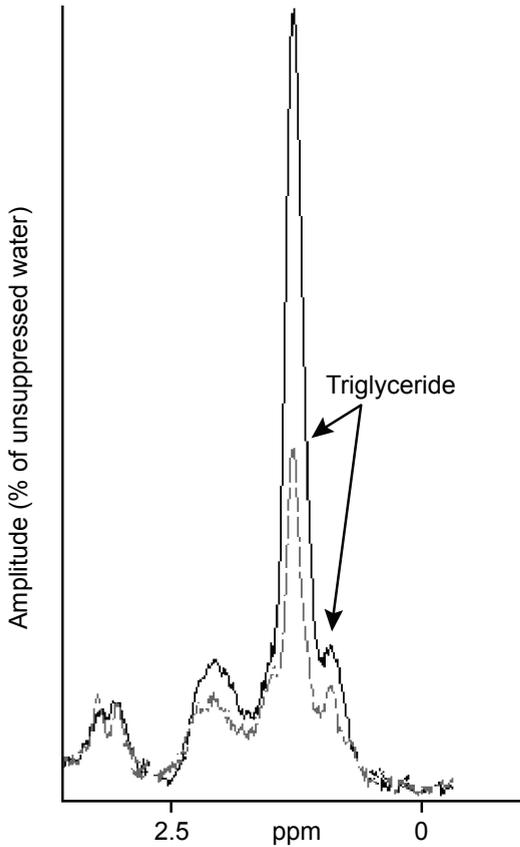


Figure 2.4

Water-suppressed magnetic resonance spectra from metabolic imaging show effect of a very low-calorie diet on triglyceride content in a healthy volunteer. Peak height is relative to the water signal in a reference spectrum without water suppression. Myocardial triglyceride peak height increased nearly twofold after a 3-day very low-calorie diet. Dashed line = baseline, solid line = very low-calorie diet, ppm = parts per million.

width at half maximum with use of the respiratory navigator technique correspond to values reported for the tibialis anterior muscle (17) and are lower than previously published values for myocardial ¹H MRS (1). Therefore, application of respiratory navigator gating and tracking improves spectral resolution for metabolic imaging of myocardial TGs of the human heart.

The mean percentages of myocardial TGs, assessed with and without respiratory motion compensation, were in accordance with previously published data from other studies (9), but with respiratory navigator, the percentage myocardial TG content was lower than the acquired values in our study without use of respiratory motion compensation.

The observed percentages of TGs are scattered over a relatively large range for all acquisition conditions. In all acquisition conditions, the CRSDs were less than 1% of the signal amplitude, and thus spectral noise was considered to have a negligible contribution to the uncertainty of our measurements. Therefore we assume that the observed range in myocardial TG percentages reflects differences in measurement conditions (i.e., presence or absence of navigator gating). The observed higher percentage of myocardial TGs without application of respiratory motion compensation is probably caused by contamination of epicardial fat. The contamination is most likely caused by the relative displacement of the acquisition volume in myocardial tissue,

due to respiratory motion causing contamination from outside the selected voxel and thereby to an increase in the apparent percentage of myocardial TGs.

Bland-Altman analysis showed improved agreement in myocardial TG assessment with use of respiratory navigator gating and tracking. No comparable data could be found in previous reports. In addition, with use of the respiratory navigator, reproducibility of myocardial TG assessment expressed as the intraclass correlation coefficient and the coefficient of variation improved significantly. In our study, use of respiratory navigator gating and tracking improved the intraclass correlation coefficient from 0.32 to 0.81 and decreased the coefficient of variation from 32.4% to 17.9% for assessment of myocardial TGs. A coefficient of variation of 17.9% for the assessment of myocardial TGs with use of respiratory motion compensation is in concordance with results of previous studies in which various other methods were used for cardiac and respiratory motion correction to increase spectroscopic quality (2;3). Szczepaniak *et al.* (3) showed a coefficient of variation for MR spectroscopic determination of myocardial TGs of 17%, with use of a pressure belt for respiratory gating, while others reported a coefficient of variation of 13% for TG determination by using double triggering based on the ECG signal (2).

In our study, an increase in myocardial TG content was found after a short-term very low-calorie diet in a healthy subject. Although this test was performed in only one volunteer, and thus is not representative of a proved finding, the result corresponds to the findings of Reingold *et al.* (9). The clinical interpretation of the above-mentioned finding needs to be established in a larger cohort study. This clinical example suggests that metabolic imaging of myocardial TG content may be a useful new tool for monitoring effects of dietary and/or medical interventions in metabolic and cardiac disorders, such as metabolic syndrome, diabetes, and myocardial lipotoxicity. Furthermore, metabolic imaging of myocardial TG content may provide new (patho-) physiologic insights of myocardial TG handling, also in relation to global and regional cardiac function.

Our study has some limitations. First, ^1HMR S was performed in healthy volunteers only. A patient who is experiencing any sort of stress due to a medical condition is possibly less cooperative with a longer acquisition time caused by the respiratory motion compensation. We think, however, that a clinical cardiac MR imaging examination time of approximately 25 minutes to acquire a cardiac spectrum is not any different from other clinical cardiac MR imaging applications. The more reliable results of respiratory motion-compensated spectroscopy compared with non-respiratory motion-compensated spectroscopy warrants the extra time investment. Second, the use of cardiac ^1HMR S currently has only limited clinical relevance. However, it is potentially a very useful tool in cardiac metabolic studies; for example, in the evaluation of diet and therapy effects. Third, ^1HMR spectra were obtained in the myocardial septum only. The use of ^1HMR S in other regions of the heart was not demonstrated. We think that the myocardial septum is the most favorable region for acquiring cardiac spectra in generalized disorders that affect the myocardium, such as diabetes mellitus. Motion in the myocardial septum is limited, and the myocardial septum is far from the free walls and from the pericardial fat, which could

contaminate the spectra. However, more work needs to be done to develop a reliable $^1\text{HMRS}$ technique for the lateral walls of the heart, which could be of interest in assessing myocardial lipid accumulation in localized disorders such as myocardial infarction.

CONCLUSIONS

Respiratory navigator-gated and ECG-triggered $^1\text{HMRS}$ of the human heart to assess myocardial TG content showed substantially better spectral resolution and reproducibility than ECG-triggered $^1\text{HMRS}$ without respiratory motion correction. Therefore, we believe that respiratory motion correction is essential for reproducible metabolic imaging of myocardial TG content of the human heart.

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