

Age Dependency of Myocardial Triglyceride Content: A 3T High-Field ^1H -MR Spectroscopy Study

Untersuchung der Altersabhängigkeit myokardialer Triglycerid-Konzentrationen mit ^1H -MR-Spektroskopie bei 3 T

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Key words

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- myocardial triglyceride content
- age dependency

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Zusammenfassung



Ziel: Die Rolle myokardialer Triglyceride (mTG) im alternden menschlichen Herz wurde bis dato noch nicht ausführlich untersucht. Das Ziel dieser Studie war die Konzentration von mTG an gesunden Probanden zu messen und Zusammenhänge zwischen Alter, mTG-Konzentration und systolischer Herzfunktion aufzuzeigen. Des Weiteren sollte die technische Zuverlässigkeit der Protonen-MR-Spektroskopie (^1H -MRS) am Herzen bei einer Feldstärke von 3 T untersucht werden.

Material und Methoden: Insgesamt 47 gesunde Probanden wurden entsprechend ihres jeweiligen Alters in 4 Kohorten unterteilt (1. Kohorte 20–29 Jahre, n=20; 2. Kohorte 30–39 Jahre, n=10; 3. Kohorte 40–49 Jahre, n=9; 4. Kohorte 50–51 Jahre, n=8). Kardiale MRT und doppelt getriggerte ^1H -MRS des Myokards wurden unmittelbar nacheinander an einem 3 T Gerät durchgeführt. Von jedem Teilnehmer wurden in einem Untersuchungsgang zwei spektroskopische Messungen akquiriert.

Ergebnisse: Der mTG Gehalt korreliert mit dem Lebensalter ($r=0,48$; $p<0,001$). Folgende altersgemittelte mTG Werte (angegeben als mTG/Wasser-Resonanz-Verhältnis in Prozent) wurden ermittelt: 1 Kohorte 0,25% ($\pm 0,17$); 2 Kohorte 0,48% ($\pm 0,30$); 3 Kohorte 0,48% ($\pm 0,18$); 4 Kohorte 0,77% ($\pm 0,70$). Die mTG-Konzentration in Gesunden ist unabhängig von der LV-Masse ($r=0,04$; $p=n.s.$) und der systolischen Herzfunktion ($r=-0,01$; $p=n.s.$) Die technische Zuverlässigkeit der ^1H -MRS des Herzens bzw. die Reproduzierbarkeit der mTG Werte waren hoch ($r=0,965$; $p<0,001$).

Schlussfolgerung: Die myokardiale TG-Konzentration bei Gesunden nimmt mit dem Alter zu. Die ermittelten mTG-Konzentrationen aus dieser Studie könnten als Orientierungswerte für Normkollektive in zukünftigen ^1H -MRS Studien herangezogen werden.

Abstract



Purpose: The role of myocardial triglyceride (mTG) content in the aging human heart is not entirely understood. The aim of this study was to measure concentrations of mTG content from healthy volunteers and to determine the association between age, mTG content and systolic heart function. Furthermore, the technical stability of the ^1H -magnetic resonance spectroscopy (^1H -MRS) and the reliability of peak evaluation at 3 T were evaluated.

Materials and Methods: The total study population of 47 healthy volunteers was divided into 4 age classes, according to the age of the subjects (1st cohort 20–29 years (yrs.), n=20; 2nd cohort 30–39 yrs., n=10; 3rd cohort 40–49 yrs., n=9; 4th cohort 50–60 yrs., n=8). Cardiac MRI and double triggered ^1H -MRS of the myocardium were consecutively performed using a 3 T scanner. Each participant underwent spectroscopic measurements twice in the same investigation.

Results: mTG content increases with age. The correlation of age and mTG is minimal ($r=0,48$; $p<0,001$). The following age-averaged mTG content values expressed as % of mTG signal compared to the water signal were determined for each cohort: 1st cohort 0.25% (± 0.17); 2nd cohort 0.48% (± 0.30); 3rd cohort 0.48% (± 0.18); 4th cohort 0.77% (± 0.70). There was no significant correlation ($r=0,04$; $p=n.s.$) between LV mass and mTG content in healthy volunteers. Within our cohorts, no effects of age or mTG content on systolic heart function were seen ($r=-0,01$; $p=n.s.$). The intra-class correlation coefficient of spectroscopic measurements was high ($r=0,965$; $p<0,001$).

Conclusion: Myocardial TG content increases with age. The normal age-dependent concentration ranges of myocardial lipid metabolites reported in this study may be helpful for the correction of acquired ^1H -MRS data in patients when evaluating metabolic and cardiovascular diseases in future magnetic resonance spectroscopy studies.

Kernaussagen:

- ▶ ¹H-MRS ermöglicht die nicht invasive myokardiale Lipid Bestimmung
- ▶ Die doppelt getriggerte ¹H-MRS des Herzens bei 3T ist eine technisch zuverlässig Methode
- ▶ Die myokardiale Triglycerid-Konzentration steigt mit dem Lebensalter
- ▶ Die myokardiale Triglycerid-Konzentration ist unabhängig von der LV Masse und LV Funktion

Key Points:

- ▶ ¹H-MRS enables noninvasive myocardial lipid determination
- ▶ Double triggered ¹H-MRS of the heart at 3T is a technically stable and reliable method
- ▶ Myocardial triglyceride content increases with age
- ▶ Myocardial triglyceride content is independent of LV mass and systolic function

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Introduction

Several studies over the last 20 years have demonstrated the potential of localized proton magnetic resonance spectroscopy (¹H-MRS) for the noninvasive assessment of myocardial lipid content [1–4]. In 2011 O'Connor et al. evinced a strong correlation ($r=0.97$) between *in vivo* (¹H-MRS) and *ex vivo* (myocardial biopsy) myocardial triglyceride (mTG) measurements. Thus, based on the high specificity of *in vivo* ¹H-MRS measurements in human myocardium, it is widely accepted that proton magnetic resonance spectroscopy provides reliable measurements of myocardial triglyceride content and is suitable for routine studies [2]. In particular, the introduction of double triggered (ECG and respiration) ¹H-MRS favors the use of this technique for cardiac examinations [5, 6].

Compared to previous 1.5T MR scanner generations, the use of ¹H-MRS at higher field strengths (3T – high-field) allows an even more precise determination of cellular metabolites, as signal intensity is augmented with higher field strength [7, 8]. In contrast, electronic noise, which originates mainly from the patient, remains constant. Thus, signal-noise ratio increases with field strength.

For the last decade, it has been known that intracellular triglycerides qualify as biomarkers for chronic diseases of the human organism [9]. Myocardial steatosis (mTG content obtained by ¹H-MRS) was shown to be an independent predictor of diastolic dysfunction in type 2 diabetes mellitus by Rijzewijk et al. [10]. *Ex vivo* as well as *in vivo* studies revealed that myocardial TG accumulates with increased body mass and, in addition, is relevant to cardiac structure and function [3].

To date, all ¹H-MRS studies of the human myocardium have compared healthy volunteers to a patient cohort with defined pathological conditions. Resulting limitations may be a mismatch within these study cohorts, such as differences in age between volunteers and patients. The increase of mTG content in patients may be influenced by the disease, i.e. advancement of pathophysiological conditions. Currently, there is only little data demonstrating the phys-

iological age dependency of myocardial TG content. Commonly, the increase of mTG content in patients is seen to be influenced by the disease only, i.e. worsening of pathophysiological conditions. Currently, there is only a small knowledgebase, demonstrating dependency of mTG content on age in males [11].

Therefore, the purpose of this study was to investigate the effects of age on mTG content in a healthy cohort and to evaluate the technical stability of the method, as well as potential inter-measurement effects of the method.

Materials and Methods**Study Subjects**

A total of 47 healthy volunteers, ranging from 22 to 60 years, were included in this prospective study. All volunteers were informed about the research status of the investigation and gave written consent. Subjects with any of the following criteria were not included in the study: 1) medicated for or diagnosed with a cardiovascular or metabolic disorder, 2) borderline or manifest hypertension, 3) pregnancy, 4) implanted devices that might limit the quality of the MR imaging and/or spectroscopy. The body mass index (BMI) of the entire study population ranged from 17.9 to 34.7 kg/m² with a mean of 24.8 kg/m².

The total study population was divided into 4 cohorts, according to the age of the subjects. The 1st cohort (age of 20–29 years) included 20 subjects (12 male, 8 female; mean age ± standard deviation, 25.8 ± 1.9 years [range: 22–29 years]). The 2nd cohort (age of 30–39 years) included 10 subjects (8 male, 2 female; 34.6 ± 2.2 years [range: 32–39 years]). The 3rd cohort (age of 40–49 years) included 9 subjects (7 male, 2 female; 45.2 ± 2.8 years [range: 40–49 years]). The 4th and oldest cohort (age of 50–60 years) included 8 subjects (6 male, 2 female; 57.2 ± 2.1 years [range: 53–60 years]). The listed age distribution and the number of subjects per group as well as gender distribution are provided in **Table 1**.

Table 1 Characteristics of the different cohorts.**Tab. 1** Charakteristika der einzelnen Kohorten.

cohort	n	range [years]	mean age [years]	male	female	mTG [%]	EF [%]	LVM [g]	CO [L/min]
1	20	20–29	25.8	12	8	0.25	64.5	132.2	6.52
2	10	30–39	34.6	8	2	0.48	62.4	122.5	6.67
3	9	40–49	45.2	7	2	0.48	60.7	129.6	6.61
4	8	50–60	57.2	6	2	0.77	59.4	150.1	6.21

mTG = myocardial triglycerides; EF = ejection fraction; LVM = left ventricular mass; CO = cardiac output.

Myocardial Magnetic Resonance Imaging and Spectroscopy

All participants underwent a fasting period of at least 2 hours prior to the investigation. Double triggered high-field cardiac ^1H -MR spectroscopy and MR imaging were performed using a 12-channel phased array body coil on a 3 T MRI unit (MAGNETOM Trio, Siemens Sector Healthcare, Erlangen, Germany) with subjects in supine position.

Cardiac MRI

Functional cardiac imaging was performed by conventional cine MRI of the short and long heart axis using a segmented two-dimensional spoiled gradient-echo sequence (field of view [FOV] adjusted individually; matrix size 256×216 ; slice thickness 8 mm; TR 3.5 ms; TE 1.48 ms; flip angle 45°). Left ventricular (LV) mass and LV function (expressed as ejection fraction [EF]) were analyzed as described previously [12]. In addition, the cardiac output (CO) was calculated by multiplying the stroke volume and heart rate (expressed in L/min.). All MRI scans were performed without the use of contrast agent.

Cardiac MRS

Cardiac ^1H -MR spectra (voxel size 6 ml) were obtained from the interventricular septum using a point-resolved spectroscopy sequence (PRESS). The voxel was positioned in the interventricular septum on the short-axis and four-chamber images (Fig. 1). Spectroscopic data acquisition was double triggered by electrocardiographic signals as well as respiratory motion gating to minimize the influence of cardiovascular and respiratory motion [5, 6]. All spectra were acquired at end-systole and end-expiration with an echo time (TE) of 35 ms and a repetition time (TR) of at least one heartbeat. 256 data points were acquired by using 2000-Hz spectral width and averaged over 32 acquisitions. In order to guarantee minimal inter-examination variability, as well as to test the technical stability of double triggered spectroscopic measurement and subsequently the reliability of peak evaluation, each participant's spectroscopic measurements were repeated, thus without changing the patients or the voxel position.

In consequence, a total of four ^1H -MR spectra (two with and two without water suppression) were collected for each observation, utilizing the proton signal from water in cardiac tissue as an internal reference for chemical shift offset and fat concentration (Fig. 2a) [3, 13, 14].

In analogy to the approach of former studies [5, 15], we summed the areas of lipid resonances at 0.9 ppm (CH_2 - methylene groups) and 1.3 ppm (CH_3 - methyl groups) (Fig. 2b, c) to assess the total mTG resonance peak area. The relative value of mTG

content was calculated as the quotient of the total mTG resonance area and the tissue water resonance area. Values are presented as percent (%).

Statistical Analysis

Normal distribution of our data was evaluated by the Kolmogorov-Smirnov test and the Shapiro-Wilk test. As EF and CO proved to be normally distributed, an independent T-test was used for evaluation, while the Mann-Whitney-U test was utilized for the evaluation of the non-normally distributed LVM and TGC to check for statistical significance. A value of $p < 0.05$ was considered significant. Statistical analyses were performed using statistical software (IBM SPSS Statistics for Mac, Version 21.0, Armonk, NY, USA).

Results



Myocardial ^1H -MRS was successfully performed in all participants.

Fig. 2b, c show typical examples of water-suppressed myocardial ^1H -MR spectra of two participants 25 years and 49 years old with normal BMI values.

Technical Stability of the Method

A total of 188 spectroscopic measurements (4 per patient) and 94 calculations of mTG water ratio (2 per patient) were conducted. The intraclass correlation coefficient was $r = 0.965$; $p < 0.001$. The results of reproducibility in mTG determination are demonstrated in Fig. 3.

Myocardial TG Content

mTG content increases with age. The correlation of age and mTG content is narrow ($r = 0.48$; $p < 0.001$). We found significantly different mean mTG content when comparing the youngest cohort with the older cohorts (cohort 1 to 2 $p = 0.001$; cohort 1 to 3 $p < 0.001$; cohort 1 to 4 $p = 0.001$), whereas no significant differences were observed between cohorts 2–4. Furthermore, a higher scattering of mTG levels was observed with increasing age, especially in cohort 4, whereas the median of mTG levels in the older cohorts was basically the same. The increase of mTG content with advancing age is demonstrated in Fig. 4a for the 4 cohorts and in Fig. 4b for the whole study population.

The following age-averaged mean mTG values were acquired (data shown in Table 1): Cohort 1 (20–29 years) 0.25% (± 0.17), [range: 0.10–0.71%]; cohort 2 (30–39 years) 0.48% (± 0.30), [range: 0.10–1.11%]; cohort 3 (40–49 years) 0.48% (± 0.18), [range: 0.23–0.87%]; cohort 4 (50–60 years) 0.77% (± 0.70), [range: 0.15–2.4%].

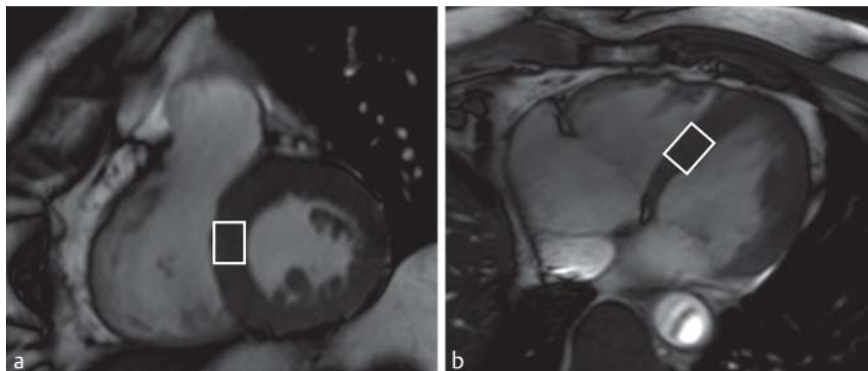


Fig. 1 Myocardial voxel location for ^1H -MRS. Voxel position in the interventricular septum on the **a** short-axis and **b** 4-chamber view.

Abb. 1 Positionierung des Voxels im interventrikulären Septum während der Endsystole in der **a** kurzen Herzachse und **b** im 4-Kammer Blick.

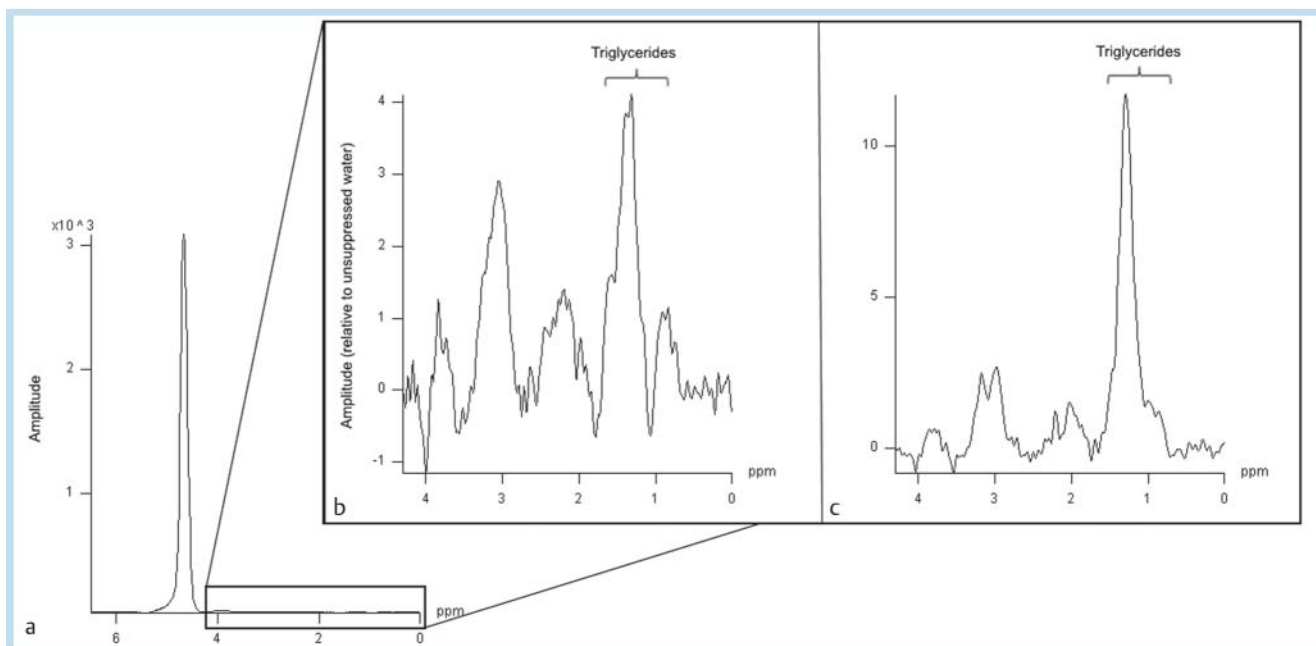


Fig. 2 Non-suppressed spectra **a** show the typical peak of tissue water set to 4.7 ppm. Image sections **b** and **c** (enlarged viewing) demonstrate typical examples of water-suppressed spectra in healthy subjects. The myocardial triglyceride (mTG) content of a 25-year-old volunteer **b** was 0.14 %, whereas the mTG content in a 49-year-old volunteer **c** was 0.63 %. Please note the different scaling of the y-axis.

Abb. 2 Beispiele von Singlevoxel-Spektren **a** ohne und **b/c** mit Wasserunterdrückung (vergrößerter Bildausschnitt) zeigen die typischen Peaks von Wasser bei 4,7 ppm und der Triglycerid-Gruppen zwischen 0,9 ppm [CH^2] und 1,3 ppm [CH^2]. Die myokardiale Triglycerid (mTG)-Konzentration eines **b** 25-jährigen Probanden war 0,14 %, während der gezeigte **c** 49-jährige Proband eine mTG-Konzentration von 0,63 % aufwies. Bitte beachten: unterschiedliche Skalierung der y-Achse.

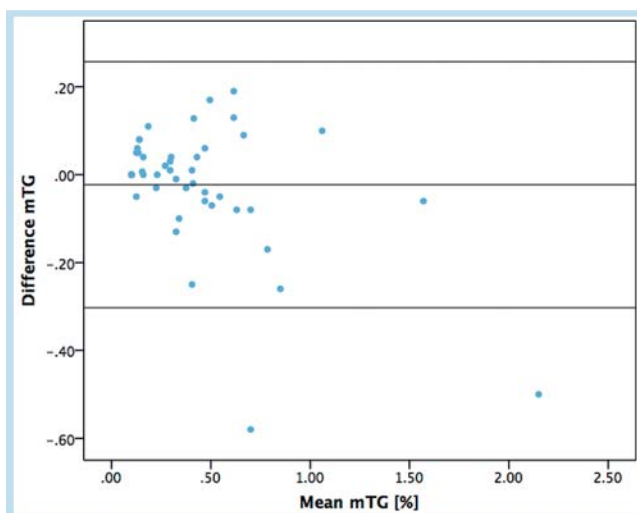


Fig. 3 Bland-Altman plot of the differences between repeated myocardial triglyceride (mTG) measurements demonstrating the high technical reliability of mTG determination using ^1H -MRS. The intraclass correlation coefficient between repeated measurements was $r = 0.965$; $p < 0.001$.

Abb. 3 Das Bland-Altman-Diagramm zeigt die gute Reproduzierbarkeit der wiederholten spektroskopischen Einzelmessungen. Der Korrelationskoeffizient zwischen den einzelnen Messungen betrug $r = 0,965$; $p < 0,001$.

While we found a slight correlation between BMI and mTG content ($r = 0.27$; $p = 0.008$), age proved to be the dominant variable accounting for higher mTG content in healthy humans.

As expected, LV mass for each individual fell within established standard values, as averaging (145 ± 65 g) in literature [3, 16, 17]. The average LV mass of our study population was 140.2 ± 36.1 g (median 134 g). We observed no significant correlation ($r = 0.04$; $p = \text{n.s.}$) between LV mass and mTG content in healthy volunteers.

Systolic Heart Function

Our data showed no relation between LV ejection fraction and mTG content in our subjects ($r = -0.01$; $p = \text{n.s.}$). Furthermore, in our study collective the systolic heart function, expressed as EF or CO, was independent with regard to age (EF: $r = -0.04$; $p = \text{n.s.}$ vs. CO: $r = -0.06$; $p = \text{n.s.}$).

Discussion

In the present study, we demonstrated that myocardial TG content increases in the aging human heart. We found a gain of mTG content with advancing age, independent of BMI.

A positive age-associated accumulation of TG in the myocardium of rodents, as well as in the myocardium of male human subjects has been shown previously [11, 18]. Furthermore, myocardial steatosis is an independent predictor of diastolic function in humans [10, 11]. Moreover, pathological conditions, such as obesity and diabetes mellitus, have been shown to be related to mTG content [10, 19].

Several possible pathways for age-associated mTG accumulation have been discussed. One explanation for rising myocardial TG concentration at an older age might be a discrepancy between myocardial uptake and myocardial oxidation of fatty acids in advanced age. Kates et al. have shown a decline of myocardial fatty

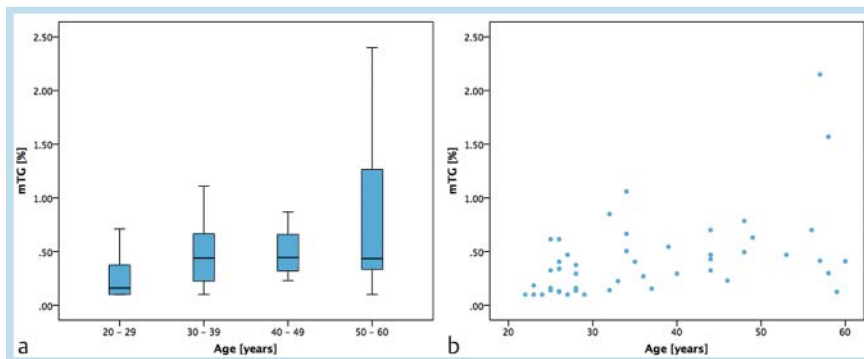


Fig. 4 Distribution of myocardial triglyceride (mTG) content expressed by percentage relative to unsuppressed water signal vs. age, categorized in cohorts **a** and as an ungrouped scatter plot **b** for the whole study population. The horizontal lines within the box plot represent median values, and the bars represent the interquartile range.

Abb. 4 Altersabhängige Verteilung der myokardialen Triglycerid (mTG) Konzentration (angegeben als mTG/Wasser-Resonanz-Verhältnis) in Prozent (**a** nach Alter eingeteilt in vier Kohorten, **b** als Streudiagramm für die gesamte Studienpopulation). Die horizontalen Linien in den Kästen zeigen Medianwerte, die Balken den Interquartilsabstand.

acid utilization and oxidation with increasing age in healthy humans [20]. Furthermore, an imbalance between tissue uptake and disposal has been demonstrated in the skeletal muscle of elder populations without health issues compared to younger subjects. The imbalance was shown to lead to an increase of intramyocellular lipids [21]. A similar mechanism in myocardial muscle might be a conceivable explanation for TG accumulation in the aging heart.

The same method – $^1\text{H-MRS}$ – was used previously for the measurement of liver fat (LFAT) in healthy volunteers. Results in different studies do not comprise a consistent picture. Tarasow et al. found no statistically significant correlation between aging and LFAT [22], while a strong increase of LFAT in advanced age was shown by Cree et al. [21].

The present study delivers age-specific mTG values in healthy human subjects. The average myocardial TG content of our whole study population ($0.44\% \pm 0.38$) confirms previously published data. McGavock et al. demonstrated nearly equal values for myocardial TG of $0.46\% \pm 0.30$ in lean subjects (mean BMI 23 kg/m^2) and $0.81\% \pm 0.46$ in obese subjects (mean BMI 32 kg/m^2) [19]. Others found similar myocardial TG values of $0.52\% \pm 0.11$ [23] in healthy volunteers (both studies used a 1.5 T scanner). We are aware of the fact that methylene (CH_2) and methyl (CH_3) groups do not represent all molecular TG groups. However, and in accordance with the approach of former studies, we limited our calculations to these two main resonances [5, 23].

Myocardial $^1\text{H-MR}$ spectra were obtained from the interventricular septum. As reported in previous studies, the interventricular septum is the most reliable region for acquiring myocardial spectra due to its limited motion. This position enables the voxel to be distant from the pericardial fat, which reduces contamination of the spectra as compared to measurements obtained from the free walls.

The rising number of $^1\text{H-MRS}$ studies reflects the necessity and power of $^1\text{H-MRS}$ as a tool for the noninvasive investigation of the myocardial metabolism in various diseases and indications. However, reliable data on age-dependent normal myocardial TG concentrations have not been reported in the literature. In the present study, age-specific values of myocardial triglycerides in cohorts ranging from 20 to 60 years of age were acquired. It is worth mentioning that there is a notable difference between the mean mTG values and the median of mTG content within cohort 4 (50–60 years).

As mentioned previously, mTG content is an independent predictor of the age-related decline of diastolic function in humans [10]. Contrary to this, systolic heart function is described to be independent of mTG content [3, 11]. Our study did not find a correlation between mTG content and systolic function ($r = -0.01$; $p > 0.05$).

Technical Stability of $^1\text{H-MRS}$

Former studies were able to show a high reproducibility of the method. In 2007, Van der Meer et al. first described the benefits of the respiratory navigator technique, which significantly improves the reproducibility of *in vivo* mTG content determination ($r = 0.32$ without navigator; $r = 0.81$ with navigator) [5]. In 2005, Reingold et al. were able to show a remarkably high test-retest reliability ($r = 0.987$) of their repetitive measurements lying 90 days apart [4]. We could validate $^1\text{H-MRS}$ as a reliable tool within a clinical routine setting. A high correlation coefficient ($r = 0.965$) is among the results of repetitive $^1\text{H-MRS}$ measurements in the present study.

Limitations

$^1\text{H-MRS}$ was performed in healthy volunteers only. By excluding subjects with a history of dyspnea or other impairing disorders, we do not face problems of non-periodic motion even in prolonged acquisition time.

There is a certain imbalance in gender distribution in favor of male subjects in this study. This might reduce the declaration of rising mTG content in aging females.

We did not apply intravenous contrast agent in our study population while this is often useful in clinical routine examinations. One must be aware of the potential increase of the water peak by gadolinium-based contrast agents when applying short echo times [24]. Upcoming ultra-fast $^1\text{H-MRS}$ sequences will enable time-saving spectroscopic measurements in patients even prior to i. v. contrast administration [25].

When performing our repetitive $^1\text{H-MRS}$ measurements to achieve data about the technical stability of the method, volunteers were not unloaded from the scanner bay between the different scans and the voxel position was neither changed nor adjusted between the measurements. Such an expanded study protocol would probably deliver information closer to the clinical situation of returning patients but was not performed in this study, which was mainly due to time-saving reasons.

Conclusion

Myocardial TG content is age-dependent and increases with age. The age-dependent concentration ranges of myocardial lipid metabolites reported in this study may be helpful for the correction of acquired ¹H-MRS data in patients when evaluating metabolic and cardiovascular diseases. However, larger studies are needed to further evaluate the role of mTG content and its physiological fluctuation within different life decades.

Clinical Relevance of the Study

- ▶ Myocardial triglyceride content is age-dependent and increases with age.
- ▶ The myocardial triglyceride content is independent of LV mass and systolic heart function.
- ▶ ¹H-MRS proved to be a highly reliable, sensitive tool for myocardial lipid determination and can be used for the evaluation of metabolic and cardiovascular diseases in future studies.
- ▶ The concentration ranges of myocardial lipid metabolites reported in this study may be helpful for the correction of acquired ¹H-MRS data in patients in future studies.

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