The ageing male heart: myocardial triglyceride content as independent predictor of diastolic function

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Aims
In animal models of obesity and diabetes mellitus, myocardial TG accumulation is associated with decreased myocardial function. In the physiologically ageing heart, myocardial triglyceride (TG) accumulation may also occur due to reduced myocardial fatty acid oxidation. The role of myocardial TG in the ageing human heart is unknown. Therefore, the purpose of our study was to evaluate the effects of ageing on myocardial TG content, and to determine the association between myocardial TG content and heart function.

Methods and results
1H-magnetic resonance spectroscopy and magnetic resonance imaging of the heart were performed in 43 healthy male subjects. Mean age (range) of the subjects was 44 (20–66) years. Body mass index (BMI), blood pressure, and biochemical markers were determined. Age correlated significantly to myocardial TG content ($r = 0.57, P < 0.05$) independently of BMI. Furthermore, myocardial TG content correlated negatively with left ventricular diastolic function (represented by E/A ratio, $r = -0.68, P < 0.05$). Multivariable analysis indicated myocardial TG content as independent predictor ($P < 0.05$) of the age related decrease in diastolic heart function.

Conclusion
Myocardial TG content increases in the physiologically ageing male heart and is associated with the age-related decline in diastolic function, independent of BMI, blood pressure, and biochemical blood markers.

Keywords
Spectroscopy • Heart • Ageing • Lipids • Heart function • MRI

Introduction
The risk of cardiovascular complications is increased in patients with type 2 diabetes mellitus.1 Despite commendable efforts to understand the pathophysiology of these co-morbidities, the exact mechanism of disease remains unknown. It is suggested that myocardial lipotoxicity plays a role in developing diabetic cardiomyopathy.2 Recently, McGavock et al.3 demonstrated increased myocardial triglyceride (TG) content in patients with diabetes. In animal models of obesity and diabetes mellitus, myocardial TG accumulation has been demonstrated to be associated with decreased myocardial function.2,4

In humans, physiological ageing is a significant risk factor for developing obesity or diabetes mellitus type 2 and is associated with a variety of complex changes in cardiovascular function.6,7 Ageing leads to a decline in diastolic left ventricular function, and increased cardiovascular stiffness partly caused by a decrease in vascular endothelial-dependent dilatation and increased endothelial oxidative stress.6,8 Furthermore, in the ageing heart, myocardial fatty acid oxidation is reduced.9 This may affect the balance between fatty acid oxidation and storage of non-esterified fatty acids (NEFA) in the form of TG in cardiomyocytes. It is postulated that NEFA taken up from the blood plasma by myocytes in excess of oxidative
effects of potential fluctuation in lipid metabolism in women on myocardial TG content, and to determine the effect of myocardial TG content on heart function using MRI techniques. In addition, hepatic and visceral fat depositions were quantitatively assessed. Imaging parameters included the following: TE = 3.5 ms. The temporal resolution was 25–39 ms depending on the heart rate, flip-angle = 50°, slice thickness = 10 mm, slice gap = 0.00 mm, field of view = 400 × 400 mm, reconstructed matrix size = 256 × 256. All images were analysed by an expert radiologist without knowledge of the subject's clinical status.

**Methods**

**Study subjects**

Volunteers for this study that was approved by the local ethics committee were recruited by advertisements in local papers. Only males were included, because the hormonal status or use of contraceptives may affect lipid metabolism in women. Given the well documented effects of oestrogens on lipid metabolism (including plasma lipid levels, adipose tissue) and the gender differences in expression of certain cell surface receptors/transporters of fatty acids, we decided to exclude women at this stage to avoid possible confounding influences of potential fluctuation in lipid metabolism in women on hepatic and myocardial TG accumulation.

Overall selection criteria were: age >18 years, no known acute or chronic disease based on history and physical examination and standard laboratory tests (blood counts, fasting plasma glucose, lipids, creatinine, alanine aminotransferase, aspartate aminotransferase), a normal electrocardiogram; no signs or symptoms of (previous) cardiovascular disease. Exclusion criteria included drug treatment, smoking, substance abuse, or hypertension. Furthermore, a 75-g oral glucose tolerance test was conducted to exclude diabetes mellitus. Moreover, homeostasis model assessment (HOMA) index was calculated as fasting plasma glucose × fasting plasma insulin/22.5.24

Based on two-tailed sample size calculation (G*Power version 3.0.8, Universitat Kiel, Germany; one correlation: difference from constant—one sample case) indicated that with a zero-hypothesis = no correlation between age and myocardial TG content, and as alternative hypothesis = a correlation of at least 0.5, when having a power of 90% and an α-level of 0.05 we had to include 37 subjects. Technical difficulties which would result in loss of data were anticipated by small oversampling. Therefore, we aimed to include more than 40 subjects. We used the same assumptions for the correlation between myocardial function and myocardial TG content. Sixty-four subjects were initially assessed for inclusion into the study. All these 64 volunteers provided written informed consent before the first screening assessments. After the first screening assessments, 20 volunteers were excluded (19 volunteers showed abnormalities in their laboratory tests; one volunteer had an abnormal electrocardiogram). The remaining 44 subjects underwent MR scanning under the same fasting conditions (6–12 h fasting). One volunteer turned out to have cardiac abnormalities during MR scanning and was therefore excluded from further analysis. Therefore, data of 43 volunteers were analysed.

**Magnetic resonance spectroscopy**

All MR/MRS studies were performed with the use of a 1.5-T whole-body MR scanner (Gyroscan ACS/N15; Philips, Best, the Netherlands) with subjects resting in the supine position. Cardiac 1H-MR spectra (volume of interest = 8 mL) were obtained from the interventricular septum (Figure 1) as described previously.17 Spectroscopic data acquisition was double triggered using electrocardiographically triggered and respiratory navigator echoes to minimize breathing influences.17,25 Spectra were acquired at end-systole, with an echo time (TE) of 26 ms and a repetition time (TR) of at least 3000 ms. A total of 1024 data points were collected using a 1000 Hz spectral width and averaged over 128 acquisitions. Without changing any parameter, spectra without water suppression with a TR of 10 ms and four averages were obtained, to be used as an internal standard.17 MRS of the liver was performed with an 8 mL voxel positioned in the liver, avoiding gross vascular structures and adipose tissue depots. Spectra were obtained using the same parameters as described above. Sixty-four averages were collected with water suppression.

All 1H-MRS data were fitted using Java-based MR user interface software (jMRUI version 2.2; developed by A van den Boogaart, Katholieke Universiteit Leuven, Leuven, Belgium)26 as described previously.17 Myocardial and hepatic TG signals at 0.9 and 1.3 ppm were analysed by using the Advanced Magnetic Resonance fitting algorithm within jMRUI.27 Myocardial and hepatic TG content relative to water were calculated as TG/water × 100.

**Figure 1** Myocardial voxel localization for 1H-MRS. Voxel position in 4-chamber (A) and short axis (B) views.
quantitatively using dedicated software (MASS®, Medis, Leiden, the Netherlands). Left ventricular ejection fraction (EF) was assessed as measure for systolic function. Furthermore, in order to obtain aortic stiffness, aortic pulse wave velocity was assessed as described earlier.19

Moreover, an electrocardiographically-gated gradient-echo sequence with velocity encoding was performed to measure blood flow across the mitral valve for the determination of left ventricular diastolic function. Imaging parameters included the following: TE = 11 ms, TR = 168 ms, flip-angle = 90°, slice thickness = 10 mm. Three consecutive transverse images were obtained during one breath hold with the middle image at a level just above the fifth lumbar vertebrae. The volumes of the visceral fat depots of all slices were calculated by converting the number of pixels to square centimetres multiplied by the slice thickness. The maximal flow rate of E, the atrial peak filling rate, which is the maximal flow rate of E, and the ratio of E and A peak filling rates (E/A). Furthermore, the peak deceleration gradient28 of E was calculated automatically. During MRI, blood pressure and heart rate were measured.

Abdominal visceral fat depots were quantified by MRI.29 A turbo spin echo imaging protocol was used and imaging parameters included the following: TE = 11 ms, TR = 168 ms, flip-angle = 90°, slice thickness = 10 mm. Three consecutive transverse images were obtained during one breath hold with the middle image at a level just above the fifth lumbar vertebrae. The volumes of the visceral fat depots of all slices were calculated by converting the number of pixels to square centimetres multiplied by the slice thickness. The total volume of the fat depots was calculated by summing the volumes of all three slices.

Statistical analysis

Statistical analysis was performed with SPSS for windows version 12.0. Data are expressed as mean ± standard deviation (SD). Correlations were calculated using Pearson’s correlation coefficients. To detect determinants of myocardial TG content univariate and multivariable linear regression analyses were performed. We studied univariate Pearson correlations between myocardial TG content and its possible predictors (age, BMI, plasma glucose, NEFA, TG, HOMA index, hepatic TG content, and visceral adipose tissue). To identify independent predictors of myocardial TG content in multivariable analysis, myocardial TG content was entered as a dependent variable and age, BMI, visceral adipose tissue, and hepatic TG content (which were all significantly correlated to myocardial TG content) were subsequently entered as independent variables into the model. Furthermore, possible confounders such as plasma NEFA, TG, and glucose were separately entered into a model with age and BMI as independent variables and myocardial TG content as dependent variable.

Secondly, to study the value of myocardial TG content as predictor of diastolic function, an identical approach was used. First, univariate correlations between E/A and its possible predictors (age, BMI, blood pressure, heart rate, plasma glucose, NEFA, TG, HOMA index, myocardial and hepatic TG content, pulse wave velocity, and visceral adipose tissue) were assessed. To identify independent predictors of E/A in multivariable analysis, E/A was entered as a dependent variable and myocardial TG content, age, BMI, visceral adipose tissue, and hepatic TG content (which were all negatively correlated to E/A in univariate analysis) were subsequently entered as independent variables into the model.

Furthermore, all known possible confounders such as plasma NEFA, TG, glucose, HOMA, diastolic blood pressure, heart rate, and pulse wave velocity were separately entered into a model with age, myocardial TG content, and BMI as independent variables.

To test the satisfaction of the basic model assumptions, scatter plots of unstandardized predictive values and residuals were created and visually inspected for gross departures from model assumptions. P < 0.05 was considered statistically significant (two-sided). To correct for multiple testing in multivariable analysis we performed Bonferroni–Holm post hoc testing.

Results

Characteristics of the subjects

Table 1 shows characteristics of the subjects. All subjects were Caucasian males with a mean age (± SD: range) of 44 ± 15; 20–66 years and BMI was 25.9 ± 3.1; 19.4–34.9 kg/m². All subjects were normotensive (mean ± SD systolic blood pressure = 118 ± 12 mmHg; mean diastolic blood pressure = 70 ± 8 mmHg) and normoglycaemic (mean plasma glucose levels = 5.1 ± 0.4 mmol/L).

Regression analyses

Myocardial and hepatic 1H-MRS were performed successfully in all participants. Figure 2 shows typical examples of myocardial 1H-MR spectra of a younger and an older volunteer. Characteristics of the studied myocardial metabolic and functional parameters are represented in Table 1. All subjects had a normal EF (mean ± SD: 59 ± 4%). Mean E/A and E deceleration peak were 1.5 ± 0.5 and 4.5 ± 1.2 mLS⁻¹ x 10⁻³, respectively. Myocardial and hepatic TG content were 0.56 ± 0.29 and 2.85 ± 2.81%, respectively.

In addition, Table 1 lists the univariate Pearson’s correlations between myocardial TG content and age, biochemical parameters, and parameters of left ventricular function. Age was significantly correlated to myocardial TG content [r = 0.57, P < 0.05; myocardial TG content (%) = 0.088 + 0.011 x age (years)]. Multivariable analysis was performed to study the association between age and myocardial TG content. Therefore, myocardial TG content was entered as a dependent variable and age, BMI, visceral adipose tissue, and hepatic TG content (which were all significantly correlated to myocardial TG content) were subsequently entered as independent variables into the model. Furthermore, possible confounders such as plasma NEFA, TG, and glucose were separately entered into a model with age and BMI as independent variables.

In all these models, only age showed a statistically significant association with myocardial TG content also after Bonferroni–Holm correction for multiple testing. Adjustment for BMI, visceral adipose tissue, hepatic TG content, and biochemical parameters had no significant effect on the association between myocardial TG content and age.

Several parameters of left ventricular function correlated significantly with myocardial TG content (Table 1). E/A, as parameter of diastolic function, showed a significant inverse correlation with myocardial TG content (Figure 3). To study the value of myocardial TG content as predictor of diastolic function, a second multivariable analysis was performed to study the association between myocardial TG content and E/A. Therefore, E/A was entered as a dependent variable and myocardial TG content, age, BMI, visceral adipose tissue, and hepatic TG content (which were all negatively
correlated to E/A) were subsequently entered as independent variables into the model (Table 2).

Furthermore, all known possible confounders such as plasma NEFA, TG, glucose, HOMA, diastolic blood pressure, heart rate, and pulse wave velocity were separately entered into a model with age and BMI as independent variables. In all these models, both myocardial TG content and age showed a statistically significant association with E/A, also after Bonferroni–Holm correction for multiple testing. Adjustment for BMI, visceral adipose tissue,

**Table 1** Mean characteristics of the volunteers and their univariate Pearson correlation coefficients to myocardial TG content, E/A, and age

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Myocardial TG content (%)</th>
<th>E/A</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 15</td>
<td>0.57 (≤0.01)</td>
<td>−0.85 (≤0.01)</td>
<td>NA</td>
</tr>
<tr>
<td>Male gender/Caucasian (%)</td>
<td>100/100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.9 ± 3.1</td>
<td>0.44 (≤0.01)</td>
<td>−0.58 (≤0.01)</td>
<td>0.56 (≤0.01)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>118 ± 12</td>
<td>−0.06 (0.69)</td>
<td>0.19 (0.23)</td>
<td>−0.25 (0.11)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>70 ± 8</td>
<td>0.25 (0.11)</td>
<td>−0.39 (0.01)</td>
<td>0.46 (≤0.01)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>59 ± 10</td>
<td>−0.01 (0.97)</td>
<td>−0.08 (0.61)</td>
<td>−0.09 (0.58)</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>5.1 ± 0.4</td>
<td>0.14 (0.41)</td>
<td>−0.33 (0.05)</td>
<td>0.37 (0.02)</td>
</tr>
<tr>
<td>Plasma non-esterified fatty acids (mmol/L)</td>
<td>0.48 ± 0.22</td>
<td>−0.11 (0.51)</td>
<td>−0.02 (0.91)</td>
<td>−0.11 (0.52)</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.11 ± 0.43</td>
<td>−0.20 (0.24)</td>
<td>0.25 (0.14)</td>
<td>−0.32 (0.06)</td>
</tr>
<tr>
<td>HOMA index</td>
<td>1.4 ± 0.8</td>
<td>−0.10 (0.58)</td>
<td>−0.19 (0.27)</td>
<td>0.08 (0.64)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>59 ± 4</td>
<td>−0.14 (0.39)</td>
<td>0.20 (0.20)</td>
<td>−0.12 (0.47)</td>
</tr>
<tr>
<td>E/A</td>
<td>1.5 ± 0.5</td>
<td>−0.68 (≤0.01)</td>
<td>NA</td>
<td>−0.85 (≤0.01)</td>
</tr>
<tr>
<td>E deceleration (mL/s² × 10⁻³)</td>
<td>4.5 ± 1.2</td>
<td>−0.46 (≤0.01)</td>
<td>0.55 (≤0.01)</td>
<td>−0.34 (0.03)</td>
</tr>
<tr>
<td>Pulse wave velocity (m/s)</td>
<td>5.1 ± 1.0</td>
<td>0.34 (0.03)</td>
<td>−0.70 (≤0.01)</td>
<td>0.77 (≤0.01)</td>
</tr>
<tr>
<td>Myocardial TG content (%)</td>
<td>0.56 ± 0.29</td>
<td>NA</td>
<td>−0.68 (≤0.01)</td>
<td>0.57 (≤0.01)</td>
</tr>
<tr>
<td>Hepatic TG content (%)</td>
<td>2.85 ± 2.81</td>
<td>0.32 (0.04)</td>
<td>−0.28 (0.08)</td>
<td>0.21 (0.19)</td>
</tr>
<tr>
<td>Visceral adipose tissue (mL)</td>
<td>229 ± 141</td>
<td>0.42 (≤0.01)</td>
<td>−0.64 (≤0.01)</td>
<td>0.66 (≤0.01)</td>
</tr>
</tbody>
</table>

Values are Pearson r (P-value).

Myocardial triglyceride content is expressed as a percentage relative to the unsuppressed water signal. E/A = ratio of maximal left ventricular early peak filling rate and the maximal left ventricular atrial peak filling rate; TG, triglycerides; HOMA, homeostasis model assessment.

**Figure 2** Typical examples of ¹H-MR spectra. Water-suppressed spectra are displayed. Myocardial triglyceride content of the younger volunteer was 0.24%, whereas myocardial triglyceride content in the 62-year old volunteer was 0.82%.

**Figure 3** Correlation between myocardial triglyceride content and E/A. Myocardial triglyceride content is expressed as a percentage relative to the unsuppressed water signal. $r = -0.68, P < 0.05$. 

Effects of ageing on myocardial TG content
Table 2 Multivariable associations between E/A and myocardial TG content

<table>
<thead>
<tr>
<th>Model</th>
<th>E/A β (95% CI)</th>
<th>P-value</th>
<th>r</th>
<th>r²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.245 (–1.665; –0.826)</td>
<td>&lt;0.001</td>
<td>0.69</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2 (model 1 + age)</td>
<td>0.541 (–0.872; –0.210)</td>
<td>0.002</td>
<td>0.88</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3 (model 2 + body mass index)</td>
<td>0.023 (–0.029; –0.017)</td>
<td>&lt;0.001</td>
<td>0.89</td>
<td>0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4 (model 3 + visceral adipose tissue)</td>
<td>0.507 (–0.843; –0.171)</td>
<td>0.004</td>
<td>0.89</td>
<td>0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 5 (model 4 + hepatic TG content)</td>
<td>0.513 (–0.852; –0.174)</td>
<td>0.004</td>
<td>0.89</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 6 (model 3): association between E/A and myocardial TG content after adjusting for age, BMI and each of following variables</td>
<td>0.009 (–0.048; 0.029)</td>
<td>0.633</td>
<td>0.000 (–0.001; 0.001)</td>
<td>0.510</td>
<td></td>
</tr>
</tbody>
</table>

- **r** and **r²** for the respective models, i.e. in model 1, with E/A as dependent and myocardial TG content as independent variable; in model 2, myocardial TG content and age are independent variables; in model 3, myocardial TG content, age, and BMI are independent variables; in model 4, myocardial TG content, age, BMI, and visceral adipose tissue are independent variables; in model 5, myocardial TG content, age, BMI, visceral adipose tissue and hepatic TG content are independent variables. In models 6 (a–g) the possible confounders are separately entered for adjustment and β- and P-values for the association between myocardial triglyceride content and E/A are displayed. TG, triglyceride; CI, confidence interval.

- *r* and *r²* values for the association between myocardial triglyceride content and E/A. After Bonferroni-Holm correction for multiple testing, associations of myocardial TG content and age with E/A remained statistically significant.

- Level of significance for the association between the separate components of the model and E/A. After Bonferroni-Holm correction for multiple testing, associations of myocardial TG content and age with E/A remained statistically significant.

- Level of significance of the model.

Discussion

In this study, we demonstrated that myocardial TG content increases in the ageing male heart and is significantly correlated to the age-related decline in diastolic left ventricular function independently of BMI, blood pressure, and biochemical blood markers. An age-associated accumulation of TG in the myocardium of rodents has been shown earlier. Furthermore, it has been demonstrated in humans that pathological processes such as obesity and diabetes mellitus are associated with myocardial TG accumulation.

In our study, multivariable analysis showed that myocardial TG accumulation is physiological in the ageing human heart, independently of BMI. In addition, age was indicated as a better predictor.
of myocardial TG accumulation than BMI, at least in healthy subjects.

A possible explanation for age-associated myocardial TG accumulation is a discrepancy between myocardial uptake and myocardial oxidation of fatty acids. Impaired fatty acid oxidation has been shown in the ageing human heart. Although there is no evidence so far for a direct link between impaired myocardial fatty acid oxidation and myocardial TG accumulation in humans, Cree et al. demonstrated in skeletal muscle that an imbalance in the normal relationship between tissue uptake and disposal of fatty acids leads to an increase of TG and intramyocellular fatty acyl intermediates in skeletal muscle of the elderly. The same mechanism may underlie myocardial TG accumulation in the ageing male heart.

Myocardial TG accumulation can be harmful to the heart. In a transgenic mouse model with increased myocardial fatty acid uptake, myocardial TG content and fatty acid intermediates were increased resulting in lipotoxicity-induced heart failure and premature death. In the present study, we showed for the first time in healthy human subjects, that myocardial TG accumulation is inversely correlated to E/A independently of age, BMI, blood pressure, aortic stiffness, or biochemical blood markers. In addition, E peak deceleration correlated negatively with myocardial TG content, however, myocardial TG content could not be indicated as an independent predictor of E peak deceleration when adjusted for biochemical markers. Finally, there was no significant correlation between myocardial TG content and left ventricular EF. These findings indicate that myocardial TG content is more closely correlated to diastolic function then to left ventricular systolic function.

Most likely, myocardial TG stores themselves are inert, but rather are a reflection of increased intracellular concentrations of fatty acid intermediates that alter myocellular structure and function by complex molecular mechanisms. Increased fatty acid intermediates, reflected clinically by increased myocardial TG content lead to myocardial lipotoxicity due to a continuous cycle of hydrolysis of the surplus TG and re-esterification of content lead to myocardial lipotoxicity due to a continuous cycle of hydrolysis of the surplus TG and re-esterification of content. During this process toxic intermediates, reflected clinically by increased myocardial TG content.

Effects of ageing on myocardial TG content

Myocardial TG accumulation can be harmful to the heart. In a transgenic mouse model with increased myocardial fatty acid uptake, myocardial TG content and fatty acid intermediates were increased resulting in lipotoxicity-induced heart failure and premature death. In the present study, we found an association between myocardial TG content and myocardial function. However, using MRI and MRS, we cannot discriminate whether there is a causal relationship between increased myocardial TG content and reduced left ventricular function. Neither can we discriminate if myocardial TG accumulation per se hampers myocardial function due to a mechanical effect, the formation of cardioxic intermediates, or by intervening in other mechanisms such as calcium handling. Further studies need to be initiated to make these distinctions since, in animal models, therapeutic interventions aiming at reduction of myocardial TG accumulation due to disturbed fatty acid metabolism have been shown to have beneficial effects on myocardial function.

Conclusion

Myocardial TG content increases in the physiologically ageing male heart and is associated with the age-related decline in diastolic function, independent of BMI, blood pressure, and biochemical blood markers.

Conflict of interest: none declared.

References