ORIGINAL ARTICLE

Cardiac steatosis in patients with dilated cardiomyopathy

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ABSTRACT

Objective Ectopic fat accumulation within and around the heart has been related to increased risk of heart disease. Limited data exist on cardiac adiposity in subjects with dilated cardiomyopathy (DCM). The aim of the study was to examine the components of cardiac steatosis and their relationship to LV structure and function in non-diabetic DCM patients.

Methods Myocardial and hepatic triglyceride (TG) contents were measured with 1.5 T magnetic resonance spectroscopy (MRS), and LV function, visceral adipose (VAT) and abdominal subcutaneous tissue (SAT), epicardial and pericardial fat by MRI in 10 non-diabetic men with DCM and in 20 controls.

Results In face of comparable intra-abdominal fat depots, myocardial TG [0.41% (0.21–2.19) vs 0.86% (0.31–2.24), p=0.038] was markedly lower and epicardial (895 mm^2±110 vs 664 mm^2±180, p=0.002) and pericardial fat [2173 mm^2 (616–3673) vs 1168 mm^2 (266–2319), p=0.039] depots were larger in patients with DCM compared with controls. In subjects with DCM, the LV global function index was decreased to a greater extent than the LV EF [21%±6 vs 34% (16–40)].

Conclusions Myocardial TG content decreased and epicardial and pericardial fat depots increased in non-diabetic subjects with DCM. Although recognised as a site of ectopic fat accumulation, the derangement of myocardial TG seems to play a specific role in the myocardial energy metabolism in congestive heart failure.

INTRODUCTION

Accumulation of excess lipids in non-adipose tissue leads to cell dysfunction or death. This phenomenon, known as lipotoxicity, may play an important role in the pathogenesis of heart failure in humans. Animal studies have provided consistent evidence that intracellular lipid accumulation in the myocardium increases LV mass, impairs LV function and promotes cardiac fibrosis and apoptosis.[1 2] Elevation of myocardial fat has detrimental metabolic consequences, including impaired lipid oxidation, oxidative stress and mitochondrial dysfunction.[3 4] This cardiac lipotoxicity is considered to reflect the deleterious effects of the accumulation of toxic lipid species and other products of free fatty acids (FFA) and intermediate lipid metabolism within myocardial tissue.

Clinical data show that both obesity and diabetes mellitus (DM) markedly increase the risk of heart failure even in the absence of ischaemic vascular disease.[5] Increasing evidence suggests that patients with DM, the metabolic syndrome and obesity accumulate excess intramyocardial lipids and exhibit decreased systolic or diastolic LV function.[6 7] However, more recent data have found conflicting results with triglycerides (TG) accumulating both in patients with and without systolic and diastolic cardiac dysfunction.[6–9]

Idiopathic dilated cardiomyopathy (DCM) is a primary myocardial disease of unknown cause characterised by LV or biventricular dilation, eccentric hypertrophy with relative wall thinning and impaired LV systolic and diastolic performance. The histopathological hallmarks of idiopathic DCM are myocyte hypertrophy (increase in myocyte length and width), interstitial and replacement fibrosis, and progressive cardiomyocyte death.[10] Idiopathic heart failure is a complex disease frequently coexisting with DM, insulin resistance and hypertension.[11]

The importance of ectopic fat accumulation in cardiovascular diseases is well established. So far, few studies have been published on the excess fat deposition in and around the heart in subjects with DCM. In one study using proton magnetic resonance spectroscopy (MRS), myocardial TG and creatine (Cr) content were assessed in different types of cardiomyopathy.[9] The authors found that myocardial Cr was lower but the TG content was similar in patients with DCM and in normal subjects. In an MRI study,[12] patients with congestive heart failure revealed a significant reduction of epicardial adipose tissue, but in the subgroup analysis, there were no differences in indexed epicardial adipose tissue between patients with ischaemic cardiomyopathy or with DCM.

The present study used MRI and MRS to examine the different components of cardiac steatosis in non-diabetic DCM patients with heart failure.

PATIENTS AND METHODS

Study population

The study population consisted of patients with DCM and controls. Inclusion criteria for patients were (1) diagnosis of DCM within 24 months prior to the enrolment, (2) no evidence of coronary artery disease assessed by coronary angiography

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and (3) global moderate-to-severe LV dysfunction and LV EF <40% by echocardiography and MRI. Patients were treated with standard individualised therapy for heart failure, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics. All patients were taking β-blockers. Two patients were treated with statins for dyslipidemia.

Subjects without DCM were selected from our cohort of non-diabetic obese men.[13] In the controls, myocardial ischaemia was excluded by means of adenosine stress perfusion MR. In the control group, two subjects were receiving medications for hypertension, two for dyslipidemia (statins) and one for both. All study subjects underwent a cardiac evaluation, including medical history, physical examination and ECG.

Exclusion criteria for both DCM patients and controls were (1) other known acute or chronic disease based on history, physical examination and standard laboratory tests (blood counts, creatinine, aspartate aminotransferase, alanine aminotransferase, NT-probrain natriuretic peptide (NT-proBNP) and thyroid-stimulating hormone), (2) type 2 DM (based on a 2 h oral glucose tolerance test), (3) significant alcohol consumption and (4) treatment with lipid-lowering therapy except for statins. Only males were included because the hormonal status or use of contraceptives modify lipid metabolism in women. Elevated liver enzymes were allowed up to four times upper limit of normal.

The study was approved by the Helsinki University Central Hospital Ethics Committee and conforms to the principles outlined in the Declaration of Helsinki. Each subject provided written informed consent.

Demographic variables and biochemical investigations

Body mass index (BMI) and waist circumference were determined as previously described.[13] Blood pressure was measured by BPM-200 (Quick Medical, Washington, USA) in the sitting position after 5 min rest, and the mean of five measurements was recorded.

Blood samples were collected after overnight fasting. Measurements of lipids and other biomarkers were analysed as previously described.[13]

Magnetic resonance imaging and LV analysis

Cardiac imaging was performed with a 1.5 Tesla whole-body MR imager (Magnetom Avanto; Siemens AG, Erlangen, Germany). A multichannel body coil was used for reception. Cine series were acquired in four-chamber, two-chamber and LV short-axis orientations during breath-hold with a retrospectively electrocardiographically gated steady state free precession gradient echo sequence. A stack of short-axis cine series (typically 12 slices) was acquired from base to apex covering the whole LV. Typical imaging parameters were TR/TE/flip angle 50 ms/1.18 ms/69°, matrix 186×220, field of view 355×420 mm, slice thickness 8 mm, gap 2 mm and temporal resolution 32–53 ms.

Volumetric analysis of the LV was scrutinised using dedicated postprocessing software (Argus, Siemens). LV end-diastolic, end-systolic, stroke volume, mass and EF were reported and volume parameters and mass were indexed to subject's body surface area. The concentric remodelling of LV was estimated as a ratio of LV mass to LV end-diastolic volume.[14] LV global function index (LVGFI) was derived from the following formula: LVGFI=[LVSV/((LVEDV+LVESV)/2+LV mass/1.05)]×100.[15] LV early diastolic peak filling rate was obtained from the LV volume versus time curve. LV end-diastolic volume normalised values of peak filling rate (PFR/LVEDV) were also reported. The LV filling curve was visually inspected to identify the plateau between the early diastolic phase caused by ventricular relaxation and the late diastolic phase, the result of atrial contraction. Resulting diastolic plateau volume was divided by end-diastolic volume and the resulting percentile was reported as the ratio of early diastole.

The distribution of visceral (VAT) and subcutaneous adipose tissue (SAT) was determined by MRI as previously described.[13] We calculated the VAT/SAT ratio as a metric of abdominal fat distribution.[16] Epicardial and pericardial fat were measured as previously described.[13]

Determination of myocardial and hepatic TG content

Myocardial and hepatic TG content were measured by MRS with a 1.5 Tesla (Magnetom Avanto; Siemens AG, Erlangen, Germany) whole-body MR imager as previously described.[13] Spectroscopic acquisition from the myocardium was triggered for respiration and cardiac pulsation.

Statistical analyses

All statistical analyses were performed with SPSS V.19.0 for Windows (SPSS, Inc, Chicago, Illinois, USA). Normality of continuous variables was analysed by the Shapiro–Wilk test. Data are presented as frequencies or percentages for categorical variables, as means±SD for normally distributed continuous variables, and as medians (range) for skewed variables. Between-group differences were assessed by paired samples t test, Wilcoxon's signed-rank test and χ^2 test as appropriate. The mean value of the different parameters in two respective control subjects was used in all analyses. A p value <0.05 was considered statistically significant.

RESULTS

Ten patients with DCM and 20 controls were equally obese and similar with respect to age. At enrolment, the patients were in stable heart failure: seven were in New York Heart Associations functional class II and three were in class III. The mean duration of heart failure for the patient group was 9 months. Four patients had a history of hypertension and four had hyperlipidaemia. Patients with DCM had lower total cholesterol, low-density lipoprotein cholesterol and fasting FFAs than controls. High-density lipoprotein cholesterol, TGs, apolipoprotein B, high-sensitivity C-reactive protein, aspartate and alanine aminotransferases were similar between the study groups. Although the fasting glucose concentrations and BMIs of the two groups did not differ, the fasting insulin and the HOMA-IR index were higher in subjects with DCM. As expected, the level of NT-proBNP was significantly higher in patients than in controls (table 1).

Differences in ectopic fat depots are demonstrated in figure 1 and table 2. In the DCM group, myocardial TG content was lower and epicardial and pericardial fat depots were larger than in the controls. Hepatic TG, VAT, SAT and the VAT/SAT ratio showed a similar pattern in the study groups.

LV mass and LV end-systolic and end-diastolic dimensions were markedly elevated and the LV EF was clearly reduced in patients with DCM compared with controls. Likewise, the LVGFI and the parameters of diastolic function were lower in subjects with DCM than in controls (table 3). For additional information, see also online supplementary data (table 1).

DISCUSSION

A novel key finding of this study is that, despite similar amounts of intra-abdominal fat depots, myocardial TG was lower and epicardial and pericardial fat depots were larger in patients with DCM compared with controls. This observation was

Table 1 Clinical and biochemical characteristics of the study groups

	DCM (N=10)	Controls (N=20)	p Value
Age (years)	52±7	50±7	0.125
Body mass index (kg/m^2)	29.8±3.0	28.6±3.5	0.123
Waist circumference (cm)	105±10	102±9	0.189
Systolic blood pressure (mm Hg)	115±18	128±9	0.063
Diastolic blood pressure (mm Hg)	73±8	83±7	0.014
Current smokers (N, %)	1 (10)	5 (25)	0.326
Total cholesterol (mmol/L)	4.33±1.00	5.28±0.78	0.013
Low-density lipoprotein cholesterol (mmol/L)	2.59±0.64	3.30±0.81	0.008
High-density lipoprotein cholesterol (mmol/L)	0.94 (0.67–1.27)	0.96 (0.66–2.32)	0.169
Triglycerides (mmol/L)	1.3 (0.8–3.2)	1.4 (0.6–5.1)	0.721
Apolipoprotein B (mg/dL)	95±29	108±24	0.144
High-sensitivity CRP (mg/L)	1.4 (0.0–50.4)	1.5 (0.2–11.8)	0.401
NT-ProBNP (ng/L)	513 (57–3000)	32 (5–151)	0.005
Fasting free fatty acids (μmol/L)	442±134	588±189	0.030
fP-ALT (U/L)	27 (11–78)	30 (18–98)	0.798
fP-AST (U/L)	35 (19–64)	31 (22–103)	0.508
fS-thyroid-stimulating hormone (mU/L)	1.41±0.88	1.42±0.58	0.965
fP-glucose (mmol/L)	5.7±0.5	5.6±0.5	0.408
fS-insulin (mU/L)	12.8±5.3	8.2±5.2	0.018
HOMA-IR index	3.3±1.6	2.0±1.2	0.018

Data are expressed as means (±SD), medians (range) or as frequencies (%). p Values from paired samples t test (normally distributed variables), Wilcoxon's signed-rank test (non-normally distributed variables) or χ^2 test (frequency data). The mean value of the different parameters in two respective control subjects was used in the analysis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; DCM, dilated cardiomyopathy; HOMA-IR, the homeostasis model assessment insulin resistance; ProBNP; pro-brain natriuretic peptide.

unexpected and as such a paradox as, in general, myocardial TG correlates well with both epicardial and pericardial fat.[13] To the best of our knowledge, this is the first study using MR technology to examine cardiac steatosis by quantifying simultaneously all three cardiac fat stores as well as to relate these data to a detailed analysis of LV structure and function in patients with DCM and controls. Notably, the two groups were carefully matched for age, BMI and waist circumference and they had similar intra-abdominal fat depots including liver fat content. In addition, myocardial ischaemia was excluded in all participants by means of coronary angiography or adenosine stress perfusion MRI. Our results support the concept that in certain metabolic states there is a disconnection in factors defining TG accumulation in cardiomyocytes versus epicardial and pericardial spaces.[17 18]

Cardiac adiposity has been associated with obesity, the metabolic syndrome and type 2 DM,[6 7 13] all of which markedly increase the risk of heart failure. To date, limited MRI data have been published on cardiac adiposity in subjects with heart failure. A study comprising 66 patients with congestive heart failure due to ischaemic cardiomyopathy or DCM and 32 controls revealed significantly reduced volume of epicardial adipose tissue in patients.[12] In the subgroup analysis, however, the volume of epicardial adipose tissue was higher in patients with DCM compared with subjects with ischaemic cardiomyopathy. Sharma *et al*[19] reported that if the body weight was normal in severe end-stage heart failure, myocardial TG content was near normal, whereas in diabetes or obesity, myocardial lipids increased significantly. In a study by Nakae *et al*,[9] no difference was observed in myocardial TG levels between non-obese subjects with DCM and normal controls. In contrast, animal models of heart failure secondary to transaortic banding under non-diabetic conditions were associated with reduced myocardial TG.[20] Our findings are in agreement with recent data reporting lower myocardial TG content in myocardial biopsy samples from subjects with severe heart failure.[21]

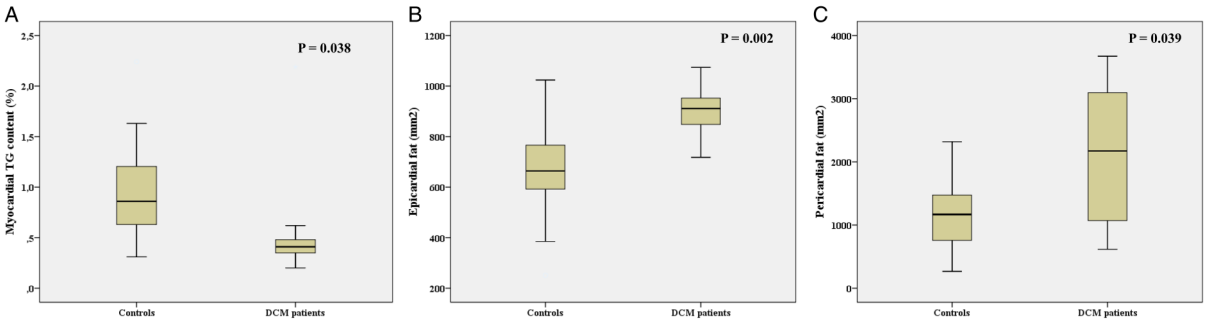

Figure 1 Box plots showing median (horizontal lines), 25th–75th centiles (boxes) and 95th centiles (whiskers) in the study groups by myocardial triglyceride (TG) content (A), epicardial fat (B) and pericardial fat (C). DCM, dilated cardiomyopathy.

Table 2 Intra-abdominal fat compartments in the study population

	DCM (N=10)	Controls (N=20)	p Value
Hepatic triglyceride content (%)	3.39 (0.40–21.61)	3.91 (0.40–8.91)	0.515
Visceral fat (cm^3)	3200 (1071–6165)	2374 (1058–5743)	0.575
Subcutaneous fat (cm^3)	4689±1805	4100±1703	0.185
Visceral fat/subcutaneous fat ratio	0.65 (0.23–1.50)	0.59 (0.26–1.31)	0.878

Data are expressed as means (±SD) or medians (range). p Values from paired samples t test (normally distributed variables) or Wilcoxon's signed-rank test (non-normally distributed variables). The mean value of the different parameters in two respective control subjects was used in the analysis.
DCM, dilated cardiomyopathy.

In a healthy heart, constant energy supply is primarily met by the β-oxidation of long-chain FAs. β-oxidation accounts for about 50–70% of the energy production of the heart, with the remainder coming from glucose and lactate oxidation.[18] As the heart has limited potential to synthesise FA, exogenous FAs are supplied to cardiomyocytes by (1) uptake of systemic FFAs originating from adipose tissue and facilitated by FA transport proteins[22] and (2) FAs derived from lipoprotein lipase-mediated hydrolysis of lipoprotein TGs. The relative importance of each of these pathways in normal and in failing heart is unclear and may vary according to the severity of heart failure.[23] In our DCM patients, the robust decrease of TG in cardiomyocytes was an unexpected finding, suggesting a severe derangement of myocardial TG metabolism. The available data support the concept that in the early stages of heart failure there is a normal or slightly elevated rate of FA oxidation, and in advanced or end-stage heart failure there is a dramatic downregulation of FA oxidation. Moreover, data support the concept that in the early stages of heart failure the myocardium primarily relies on enhanced uptake of FA as an oxidative substrate, and that there is not yet a switch to greater glucose oxidation and less FA oxidation.[23] In line, our DCM subjects showed decreased levels of plasma FFAs.

Data on lipoprotein lipase-deficient patients suggest that lipoprotein-derived FAs, and not just circulating FFAs, may be an important source of cardiac energy.[24] Recent data from animal models suggest that lipoprotein lipase activity is required for cardiac lipid droplet formation.[25]

TG content in cardiac lipid droplets can be modulated by adipose tissue TG lipase regulated by perilipin 5[26] and hormone-sensitive lipase.[27] In mice, cardiomyocyte-specific overexpression of adipose tissue TG lipase protects against increases in intramyocardial TG.[28] TG accumulation in lipid droplets may initially serve as a sink buffering against the toxic lipid species by channelling FAs away from non-oxidative toxic pathways. During ischaemia, reduced FA oxidation could foster the build-up of FA intermediates (diacylglycerols and ceramides) in the cytoplasm instead of lipid droplets, thus contributing to lipotoxicity. The mechanisms involved in the accumulation of these lipid intermediates remain obscure.

The exaggerated lipolysis of cardiomyocyte TG driven by sustained stimulation of adrenergic system to provide substrate for FA oxidation to maintain energy balance may contribute to the reduction of cardiomyocyte TG pool. In our data, the cardiomyocyte TG pool was not tightly coupled with epicardial and pericardial fat or intra-abdominal ectopic fat depots, suggesting that it may rather be more closely regulated by the state of cardiac energy metabolism and insulin resistance. Further studies on myocardial TG turnover are needed to answer the unresolved issues.

Besides the myocardial imbalance of glucose and FA metabolism, patients with heart failure develop systemic insulin resistance. In line with previous observations, we found that HOMA-IR and fasting insulin levels were elevated in subjects with DCM indicating insulin resistance. Chokshi *et al*[21] reported that systemic insulin resistance in heart failure was accompanied by decreased myocardial TG and overall FA content but increase of toxic lipid intermediates, diacylglycerols and ceramides.

Our DCM subjects showed very high values for LV end-diastolic volume, but their LV mass did not increase to the same degree. This resulted in lower LV remodelling index, indicating the eccentric remodelling caused by massive volume overload and progressive chamber dilation without compensatory wall thickening. The most frequently used index of LV function in clinical practice, the LV EF, does not account for the relationship between LV mass and dimension. Recently, an LVGFI has been introduced as a novel parameter to integrate LV structure with global function.[15] An LVGFI value <37% has been associated

Table 3 LV structure and function in the study population

	DCM (N=10)	Controls (N=20)	p Value
Systolic function and dimensions			
LV end-systolic volume (mL)	194 (108–274)	55 (25–83)	0.005
LV EF (%)	34 (16–40)	61 (50–71)	0.005
LV global function index (%)	21±6	40±5	<0.001
LV mass (g)	188±32	123±23	<0.001
LV mass/$height^{2.7}$	39±8	25±5	0.001
Diastolic function and dimensions			
LV end-diastolic volume (mL)	293 (180–353)	142 (86–214)	0.005
Peak filling rate (mL/s)	409±197	510±180	0.244
Peak filling rate/LV end-diastolic volume (s^{-1})	1.5±0.6	3.5±1.1	<0.001
LV early diastole (%)	51±13	69±11	0.003

Data are expressed as means (±SD) or medians (range). p Values from paired samples t test (normally distributed variables) or Wilcoxon's signed-rank test (non-normally distributed variables). The mean value of the different parameters in two respective control subjects was used in the analysis.
DCM, dilated cardiomyopathy.

with a significant risk of cardiovascular events. Notably, in our subjects with DCM, the LVGFI was decreased to a greater extent than the LV EF.

Study limitations

A limitation of the study is the lack of a completely normal control population, and the data showed some degree of overlap between patients and controls in cardiac lipid storages. However, age, BMI and waist circumference were comparable between the study groups. Gender may influence the magnitude of cardiac steatosis. As the number of DCM patients was small, due to the strict selection criteria and the complexity of the protocol, this can be considered as a pilot study. Consequently, the lack of statistical power limited any correlation analysis in the two separate groups. Current technical limitations restrict ^{1}H-MRS to the interventricular septum, where the cardiac motion is moderate enough to allow precise voxel placement. If myocardial fat distribution were heterogeneous in DCM, the septum would not be representative of global myocardial TG. Recently, however, Liu *et al*[29] have shown in an ex vivo study that the septum is quite representative of the overall heart fat distribution. Finally, as the study design is cross-sectional, observational inferences of causality remain limited.

CONCLUSION

This pilot study is the first to investigate cardiac steatosis in a group of non-diabetic patients with heart failure caused by DCM. We report a discrepancy between myocardial TG content and epicardial and pericardial fat depots in non-diabetic obese subjects with DCM. Reduced myocardial TG, in face of excess other ectopic fat depots, suggests a severe derangement of TG metabolism in myocardium in congestive heart failure.

Key messages

What is already known on this subject?
Increasing evidence suggests that patients with diabetes mellitus, the metabolic syndrome and obesity accumulate excess intramyocardial lipids and exhibit decreased systolic or diastolic function.

What this study adds?
This is the first study using MR technology to examine cardiac steatosis by quantifying simultaneously all three cardiac fat stores as well as to relate these data to a detailed analysis of LV structure and function in patients with dilated cardiomyopathy (DCM) and controls. A novel key finding of this study is that, despite similar intra-abdominal fat depots, myocardial triglyceride (TG) was markedly lower and epicardial and pericardial fat depots were larger in patients with DCM compared with controls.

How might this impact on clinical practice?
Although myocardial TG is recognised as a site of ectopic fat accumulation, it seems to play a specific role in the myocardial energy metabolism in congestive heart failure.

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Contributors All authors have contributed significantly to this work including the following: (1) the conception and design of the study; (2) analysis and interpretation of the data; (3) revising; and (4) final approval of the manuscript. The coauthors have read the manuscript and approved its submission to *Heart*.

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Competing interests None.

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Heart

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