The myocardium of patients with type 2 diabetes mellitus (T2D) loses its metabolic flexibility because of elevated circulating free fatty acid (FFA) levels and myocardial lipid content (MyLC). This creates a state of lipotoxicity that compromises contractile function and promotes heart failure (HF).

These processes are reversible by interventions that reduce FFA fluxes. MyLC, as measured by magnetic resonance proton spectroscopy (MRS), is increased in patients with T2D and normal left ventricular ejection fraction (LVEF), and a reduction in MyLC through caloric restriction improves diastolic function. These observations suggest that short-term suppression of circulating lipid may have adverse cardiac effects in patients with symptomatic HF, especially in patients with elevated lipid levels such as in T2D. However, the impact of high as opposed to low circulating levels of FFA on MyLC and cardiac function in patients with T2D and HF is unknown.

Clinical Perspective on p 852

We hypothesized that (1) short-term extreme changes in FFA and triglyceride levels affect MyLC in patients with T2D and HF, and that (2) suppressed as opposed to increased circulating FFA and triglyceride increase myocardial contractility and cardiopulmonary exercise capacity. The aim of the present
study was hence to investigate the impact of short-term manip- 
ulation of circulating FFA and triglycerides on MyLC, cardiac 
systolic and diastolic function, and stress-induced contractile 
reserve, and the correlation between changes in MyLC and 
contractile function.

Patients with T2D and HF were included in a random- 
ized crossover–designed trial. They underwent 8 hours of 
intralipid/heparin infusion (high FFA) and hyperinsulinemic-
euglycemic clamping (low FFA). We used advanced echo- 
cardiography, cardiopulmonary exercise testing, and MRI to 
measure cardiovascular function and MRS to quantify MyLC.

Methods

Patients

We included 20 noninsulin-treated white male patients with T2D 
and chronic HF. The patients were stable on optimal HF medication, 
in New York Heart Association class 2 to 3 and had a LVEF ≤45% 
assessed by echocardiography. We excluded patients with high age 
(>85 years), cardiac valve disease, physical or psychological dis- 
ability, creatinine >220 mmol/L, alanine aminotransferase >3-fold 
the upper normal limit, or myocardial infarction within the past 3 
months. MyLC was measured in the interventricular septum by 
MRS. Thus, we excluded patients with large septal scars visualized 
by echocardiography.

Design

All patients were investigated in a randomized crossover– 
designed trial on 2 different occasions 1 to 6 weeks apart. They 
were assigned by the investigators to either high FFA followed by low FFA 
or the opposite (one to one) by drawing sealed envelopes. Patients 
were studied in the fasting state after 8 hours of hyperinsulinemic- 
euglycemic clamping at plasma glucose of 5 mmol/L using 0.8 mU 
insulin/kg per minute. (Actrapid, Novo Nordisk, A/S, Denmark; low 
FFA) and after 8 hours of infusion of Intralipid 20% (Fresenius Kabi 
AB, Uppsala, Sweden) at 40 mL/h combined with 250 U/h of heparin 
(high FFA). To avoid bias from other antidiabetics, we chose to in- 
struct all participants to pause oral antidiabetic medication 2 days be- 
fore the investigations. Patients were admitted at 7:45 AM and venous 
cannulas were inserted into each of the upper extremities for infusion 
and blood sampling. Infusions were initiated at 8:15 AM (±10 hours) 
and continued throughout the day of investigation. In the low-FFA 
arm, plasma glucose concentration was measured every 10 minutes, 
and isotonic saline was administered with an individual variable 20% 

Blood Samples

Plasma glucose measurements were performed using HemoCue 
Glucose 201 (Angelholm, Sweden), which measures whole blood 
glucose and calculates plasma glucose. Additional blood samples 
were immediately cooled, spun, and stored at −80°C until analysis. 

Blood pressure, heart rate, and ECG were measured repeatedly every sec- 

Magnetic Resonance Investigation

A Philips 1.5 Tesla scanner and a 5-element cardiac coil were used. 
All MRI measurements were ECG-triggered and breath-hold 
was applied. MRI of the 4-chamber, the 2-chamber, and 12 slices with 
short-axis views was performed. Global left ventricular function 
was quantified using Segment v1.8 R0680 (http://segment.heiberg.se). 
We applied respiratory gating and ECG triggering to perform MRS 
and a region of interest (ROI) of 8 cm³ (4×2×2 cm) was placed to cover 
the interventricular septum avoiding epicardial lipid deposits and the 

Exercise Testing

A ZAN600 CPET (nSpire Health GmbH, D-97723 Oberthulba, 
Germany) was used. Patients performed a staged exercise bicycle 
test with stages lasting 1 minute and increments of 10 W/min. Blood 
pressure, heart rate, and ECG were measured repeatedly every sec- 

Echocardiography

Echocardiography was performed by a single operator using a Vivid 
Seven ultrasound scanner (GE Medical System, Horten, Norway) 
with a 2.5-MHz transducer. Sonovue (Bracco,init's Medical AB, 
Copenhagen, Denmark) was administered intravenously as previ- 
ously described to enhance the left ventricular endocardial border 
delineation. EchoPAC 11 software (GE-Vingmed Ultrasound, 
Horten, Norway) was used for analysis. LVEF was measured using 
the biplane-modified Simpson method. Peak systolic longitudinal 
mitral plane velocities during ejection phase (S′max) were measured 
by tissue Doppler imaging and global strain by 2D speckle track- 

Outcomes

Primary end points were defined as changes in MyLC. Secondary 
end points were changes in LVEF; myocardial contractile function 
(S′max and global strain), peak exercise capacity, oxygen consump- 
tion, postexercise LVEF, and contractile function. The outcomes 
were measured consecutively and analyzed after completion of the 
last patient.

Statistics

We applied D’Agostino and Pearson omnibus normality test. E/A-
ratio (rest, P value=0.02; exercise, P value <0.001) and time from 

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last coronary angiography \( (P=0.02) \) did not pass this normality test and are, therefore, presented as median (25%–75% percentile). All other values are presented as mean±SD. \( P \) values \(<0.05\) were considered significant. Paired \( t \) test or Wilcoxon signed rank test was used to analyze data between study arms. Spearman was used to test for correlations. Two-way ANOVA with repeated measurements and robust clustered variance analysis were used when stated. Confidence intervals of 95\% are presented when appropriate. On the basis of prior or studies,10,11 a crossover design with 20 patients, an expected drop out of 10\%, a significance levels of 5\%, and a power of 80\%, we expected to be able to detect changes in left ventricular contractility (S′ max, strain) of 6\% (in relative percentage) and LVEF of 4\% (in absolute percentage). The coefficient of variation of myocardial MRS in healthy subject is 18\%.4 Applying these parameters and complete data sets on \( \geq 10 \) patients, we would expect to be able to detect differences of 18\% in MyLC.

### Ethics

Data were collected according to the protocol at the Department of Cardiology, Department of Endocrinology and Metabolism, and the MR-Center at Aarhus University Hospital, Aarhus, Denmark. The protocol was approved by the Central Denmark Region Committee on Health Research Ethics and informed written consent was obtained from each patient.

### Results

#### Patients

Forty-three patients from our outpatient HF clinic were eligible and they were screened for inclusion between 2010 and 2011. Twenty-three were excluded either because they did not meet the inclusion criteria \( (n=21) \) or because they met the exclusion criteria according the protocol \( (n=2) \). Twenty patients were enrolled. One experienced cardiac arrest before the first visit (allocated to high FFA followed by low FFA) and another did not attend the first visit and withdrew consent (allocated to low FFA followed by high FFA). Eighteen patients completed echocardiography and exercise and postexercise echocardiography on both occasions. Patients were aged 67±7 years, had an LVEF of 35±8\%, and were in New York Heart Association class 2 or 3. The HF symptoms were because of either ischemic heart disease \( (n=15) \) or dilated cardiomyopathy \( (n=3) \). Two patients had atrial fibrillation as comorbidity. The mean duration of T2D was 5±4 years and HbA1c was 6.8±1.5\%.

All patients were on optimal medical HF treatment. Fourteen patients were on oral antidiabetic treatment and 4 patients on dietary treatment. Twelve patients completed the MRI and 10 patients completed cardiac MRS on both occasions. Drop-outs from the MR analysis were because of patients having a pacemaker \( (n=3) \), claustrophobia \( (n=2) \) during the scan, incomplete cardiac MR data \( (n=1) \), or technical problems during the myocardial MRS \( (n=2) \). No coronary angiography was performed before enrollment. However, all but 1 patient was subjected to angiography within the past 3 years \( (7 \text{ [5–13] months; median, 25%–75%] } \) which included or documented full revascularization of the arteries supplying the septum. The last patient underwent coronary angiography 5 years before enrollment and was diagnosed with dilated cardiomyopathy (Table 1; Figure 1).

#### Substrates and Hormones

FFA levels differed \( \geq 20\text{-fold} (0.05±0.04 \text{ mmol/L [low FFA]} \) versus \( 1.04±0.27 \text{ mmol/L [high FFA]} \); \( P<0.001 \) and triglycerides \( =4\text{-fold} (1.0±0.8 \text{ mmol/L [low FFA]} \) versus \( 3.9±2.0 \text{ mmol/L [high FFA]} \); \( P<0.001 \) between the study arms. Insulin levels were lowest during high FFA \( (521±244 \text{ pmol/L [low FFA]} \) versus \( 66±35 \text{ pmol/L [high FFA]} \); \( P<0.001 \), and plasma glucose levels were highest during high FFA \( (5.7±0.5 \text{ mmol/L [low FFA]} \) versus \( 9.4±4.8 \text{ mmol/L [high FFA]} \); \( P<0.01 \). C-peptide \( (P<0.001) \), glucagon \( (P<0.001) \), and ketones \( (P<0.001) \) were higher and GH \( (P<0.01) \) lower in the high-FFA arm (data not shown). Insulin-like growth factor 1 \( (P=0.34) \), cortisol \( (P=0.82) \), noradrenalin \( (P=0.29) \), adrenalin \( (P=0.27) \), and N-terminal probrain natriuretic peptide \( (P=0.29) \) did not differ between the study arms (data not shown). All patients had fasting plasma glucose \( \geq 7 \text{ mmol/L} \). Weight \( (91±12.3 \text{ kg [low FFA]} \) versus \( 90.5±12.9 \text{ kg [high FFA]} \); \( P=0.09 \), intravenous volume infused \( (899±333 \text{ mL [low FFA]} \) versus \( 761±150 \text{ mL [high FFA]} \); \( P=0.06 \), and plasma volume calculated as previously described11 did not differ significantly between the study arms \( (P=0.09) \) before the investigations.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>67±7</td>
</tr>
<tr>
<td><strong>NYHA 2/NYHA 3 (n)</strong></td>
<td>16/2</td>
</tr>
<tr>
<td><strong>IHD (n)</strong></td>
<td>15</td>
</tr>
<tr>
<td><strong>DCM (n)</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Atrial fibrillation (n)</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>LVEF, %</strong></td>
<td>35±8</td>
</tr>
<tr>
<td><strong>Systolic BP, mmHg</strong></td>
<td>129±18</td>
</tr>
<tr>
<td><strong>Diastolic BP, mmHg</strong></td>
<td>73±7</td>
</tr>
<tr>
<td><strong>Heart rate, beats per minute</strong></td>
<td>59±10</td>
</tr>
<tr>
<td><strong>Duration of diabetes mellitus, y</strong></td>
<td>5±4</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>91±13</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>6.8±1.5</td>
</tr>
<tr>
<td><strong>Plasma glucose, mmol/L</strong></td>
<td>9.6±4.5</td>
</tr>
<tr>
<td><strong>Insulin, pmol/L</strong></td>
<td>76±31</td>
</tr>
<tr>
<td><strong>C-Peptide, pmol/L</strong></td>
<td>1454±567</td>
</tr>
<tr>
<td><strong>FFA, mmol/L</strong></td>
<td>0.44±0.16</td>
</tr>
<tr>
<td><strong>Triglycerides, mmol/L</strong></td>
<td>1.4±0.9</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; BP, blood pressure; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; DPP4, dipeptidyl peptidase-4; FFA, free fatty acid; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association classification.
MR Spectroscopy
MyLC differed by 50% between the study arms (0.78±0.59% versus 1.16±0.73%; P=0.006; Figure 2). LVEF and MyLC displayed an inverse relation (r=−0.54; r²=0.29; P=0.004; Figure 3). MyLC correlated positively with FFA (r=0.45; r²=0.20; P=0.001; Figure 4A) and triglycerides (r=0.47; r²=0.22; P=0.003; Figure 4B). However, these 2 correlation did not differ (P=0.08). We identified an outlier with regard to the triglyceride levels by Grubb test. Including these data did not affect the level of significance. MyLC and insulin were negatively associated (r=−0.32; r²=0.10; P=0.04; Figure 4C). The homeostasis model assessment index, C-peptide, glucose, HbA1c, body mass index, age, and N-terminal probrain natriuretic peptide levels did not correlate with MyLC (data not shown).

Left Ventricular Function, Contractility, and Resting Hemodynamics
No differences between the study arms were observed in LVEF (ΔLVEF=±6%; confidence interval, −4% to 2%; P=0.60 [echocardiography] and ΔLVEF=±4%; confidence interval, −3% to 2%; P=0.64 [MRI]), strain, or cardiac output. S’max was higher during high FFA than during low FFA, and MAP was highest during high FFA. Diastolic parameters did not differ between high and low FFA (Table 2).

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**Figure 1.** CONSORT diagram. FFA indicates free fatty acid.

**Figure 2.** Myocardial lipid content (MyLC) expressed as percentage of water content measured by magnetic resonance proton spectroscopy. MyLC differed significantly between the study arms (*P=0.006; black dots, low free fatty acid [FFA]; white squares, high FFA).

**Figure 3.** Correlation of left ventricular ejection fraction (LVEF) and myocardial lipid content (MyLC) illustrating a negative association between LVEF and MyLC (black dots, low free fatty acid [FFA]; white squares, high FFA).
Exercise Test, Hemodynamics, and Postexercise Echocardiography

Exercise capacity, MAP, peak O2 consumption, LVEF, S’max, and strain post exercise did not differ between study arms and neither did the diastolic parameters. The respiratory equation ratio was significantly higher during rest and peak exercise in the high-FFA arm than in the low-FFA arm. Because of the placement of the ROI during MRS, we measured regional septal strain from rest to exercise and found it to increase (P=0.02; 2-way ANOVA with repeated measurements; Table 2).

Discussion

In patients with T2D and HF, MyLC displayed much flexibility in response to variations in circulating lipids and correlated inversely with LVEF and positively with FFA and triglyceride levels. Short-term elevated as opposed to suppressed FFA and triglyceride levels had no detrimental effect on LVEF, strain, exercise-induced contractile reserve, or cardiopulmonary exercise capacity. In contrast, a minor increase in S’max was observed during high lipid levels. These findings suggest that short-term lowering of circulating lipid levels and MyLC has no overt beneficial effect on left ventricular function.

Short-term Modulation of Circulating FFA in Patients With T2D and HF

FFA and myocardial lipid accumulation have been implicated in the progression of HF.1,2,14 The present study addresses the clinical and functional effects of extreme differences in FFA and triglycerides in patients with T2D, reduced LVEF, and symptomatic HF. Studies in HF patients without T2D have shown either neutral7,15 or even potentially detrimental effects of suppression in circulating FFA levels on left ventricular function and cardiac efficiency.16,17 These discordant results may reflect differences in the pathophysiology of patients with and without diabetes mellitus and differences in the severity of the metabolic derangement such patients undergo.18 The FFA levels differed >20-fold and triglyceride levels 4-fold between the study arms. Even so, we detected no significant deterioration in our end points of LVEF, cardiac output, strain, diastolic function, contractile reserve, or cardiopulmonary exercise capacity during high FFA as opposed to low FFA. In contrast, we observed a minor, but significant increase in S’max in patients with high circulating levels of FFA and triglycerides. This could be because of the fact that S’max is more reproducible19 and more sensitive to subtle contractile changes than LVEF, even by contrast-enhanced echocardiography.6 Furthermore, the present changes in S’max may have clinical relevance as it has been shown to be an independent predictor of mortality.20

Our findings seem unlikely to be caused by changes in after or preload. We would have expected the increase in MAP (and hence afterload) during high FFA to decrease S’max,21 but the opposite was observed. Although weight and plasma volume did not differ significantly between the study arms, more fluid tended to be infused during low FFA (≈140 mL; near-significant [P=0.06]) than during high FFA. This could potentially have decreased the differences in S’max between the study arms as a volume challenge increases S’max in patients with cardiac disease.22 However, the difference in volume was negligible. Furthermore, we would have expected these potential differences in volume load, if present, to affect preload and thus e’,23 however, this was not observed. Our finding seems not to be explained by a confounding effect of insulin stimulation on the sympathetic nervous system24 because insulin levels were lower during high FFA than during low FFA, the heart rate was unchanged, and catecholamine levels did not differ between the study arms. Furthermore, no evidence
Table 2. Echocardiographic, Hemodynamic, and Cardiopulmonary Exercise Parameters

<table>
<thead>
<tr>
<th>Systolic function</th>
<th>Low FFA Mean±SD</th>
<th>High FFA Mean±SD</th>
<th>P Value</th>
<th>Low FFA Mean±SD</th>
<th>High FFA Mean±SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>38±7</td>
<td>38±10</td>
<td>0.61</td>
<td>42±9</td>
<td>41±10</td>
<td>0.34</td>
</tr>
<tr>
<td>Strain, %</td>
<td>-11.1±2.5</td>
<td>-11.3±2.7</td>
<td>0.45</td>
<td>-12.4±3.6</td>
<td>-11.8±3.4</td>
<td>0.24</td>
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<tr>
<td>Cardiac output, L/min</td>
<td>5.0±1.3</td>
<td>5.1±1.2</td>
<td>0.67</td>
<td>6.7±1.9</td>
<td>7.4±1.8</td>
<td>0.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diastolic function</th>
<th>Low FFA Mean±SD</th>
<th>High FFA Mean±SD</th>
<th>P Value</th>
<th>Low FFA Mean±SD</th>
<th>High FFA Mean±SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-velocity, m/s</td>
<td>0.73±0.23</td>
<td>0.72±0.25</td>
<td>0.44</td>
<td>0.84±0.26</td>
<td>0.86±0.23</td>
<td>0.53</td>
</tr>
<tr>
<td>E/e ratio</td>
<td>264±112</td>
<td>258±111</td>
<td>0.75</td>
<td>218±91</td>
<td>210±84</td>
<td>0.70</td>
</tr>
<tr>
<td>E/A ratio*</td>
<td>20±9</td>
<td>19±9</td>
<td>0.46</td>
<td>18±9</td>
<td>18±8</td>
<td>0.52</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>1.2 (0.8–2.2)</td>
<td>1.1 (0.7–2.1)</td>
<td>0.06</td>
<td>1.1 (0.7–1.6)</td>
<td>1.3 (0.8–1.6)</td>
<td>0.09</td>
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<tr>
<td>Exercise testing</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>80±28</td>
<td>88±23</td>
<td>0.11</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87±14</td>
<td>92±11</td>
<td>0.03†</td>
<td>96±21</td>
<td>99±17</td>
<td>0.13</td>
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<tr>
<td>Heart rate, beats per minute</td>
<td>62±12</td>
<td>65±13</td>
<td>0.08</td>
<td>108±26</td>
<td>110±22</td>
<td>0.32</td>
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<tr>
<td>RER</td>
<td>1.00±0.07</td>
<td>0.86±0.03</td>
<td>&lt;0.001†</td>
<td>1.18±0.07</td>
<td>1.10±0.08</td>
<td>0.001†</td>
</tr>
<tr>
<td>Exercise capacity, W</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>102±32</td>
<td>102±32</td>
<td>0.74</td>
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<tr>
<td>O2 used, mL/min per kilogram</td>
<td>3.5±0.9</td>
<td>3.5±1.1</td>
<td>0.94</td>
<td>15.4±4.8</td>
<td>14.9±5</td>
<td>0.26</td>
</tr>
</tbody>
</table>

FFA indicates free fatty acid; IVRT indicates isovolumetric relaxation time; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NA, not available; and RER, respiratory equation ratio.

*Did not pass normality testing. Values are reported as median (25–75 percentile) and P values are calculated by Wilcoxon signed rank test.
†Parameters that differ significantly between study arms.

supports that GH or glucagon,25,26 which differed between the study arms, could have caused the observed effects in MyLC or S’max. However, differences in circulating GH concentrations could have diminished the difference in S’max as GH increases myocardial contractility.25 C-peptide differed between the study arms, but increased C-peptide levels have no vascular effects during preserved endogenous C-peptide production.27 Because all patients in the present study had preserved endogenous C-peptide production in both study arms, it is unlikely that different C-peptide levels biased our results. This suggests that the observed differences in S’max between the study arms may have been caused by intrinsic myocardial metabolic changes. Our findings supplement the observations by Tuunanen et al,16 who reported that both glucose and FFA concentrations during hyperglycemia and elevated FFA as previously shown29 could suggest that a major decrease in lipid load may be detrimental in patients with T2D and HF.

**Short-term Modulation of MyLC in Patients With T2D and HF**

Observational studies in patients with T2D and normal LVEF demonstrate that elevated MyLC correlates inversely with diastolic function and systolic strain.36 MyLC measured in myocardial biopsies is also elevated in patients with reduced LVEF because of aortic stenosis37 and end-stage dilated cardiomyopathy,32 and it is even more elevated in case of coexisting T2D.31,32 Although we were unable to detect differences in LVEF and exercise capacity between high and low circulating FFA concentrations, we demonstrated an inverse correlation between LVEF and MyLC. However, it is unknown whether this correlation reflects causality. The ability to accumulate MyLC in HF may serve as a protective buffer against detrimental lipid intermediates,33 it may give rise to decreased energy metabolism and accumulation of toxic lipid intermediates,36 or it may merely constitute an energy store when excess FFA is taken up by the cardiomyocyte. Thus, this finding of an inverse correlation between LVEF and MyLC needs to be addressed in future long-term studies. However, such studies should be carefully monitored as we observed a small, but significant decrease in S’max during reduced MyLC.

In the present study, the extreme differences in circulating FFA and triglyceride levels caused a difference of 50% in MyLC between the study arms. This indicates that MyLC...
remains flexible to short-term extreme changes in whole-body substrate supply in patients with T2D and HF. This magnitude of change in MyLC is similar\(^4\) or even greater\(^2\) than that observed in previous studies of non-HF patients, and it is in accordance with findings of a high myocardial FFA uptake in case of impaired glucose tolerance.\(^{33}\)

FFA, triglyceride levels, and MyLC correlated positively. In contrast, a previous study showed that MyLC did not increase because of elevated triglycerides 4 hours after oral lipid intake in normal test subjects.\(^6\) However, recently it was shown that in patients with impaired glucose tolerance as compared with healthy test subjects, postprandial myocardial lipid uptake is increased, although FFA levels decrease while triglyceride levels increase.\(^{35}\) This suggests that results on myocardial lipid metabolism obtained in healthy subjects are not readily transferred to patients with metabolic derangement.

The present study shows that the metabolic disturbances have not reached an end stage that eliminates the flexibility of lipid storage in patients with T2D and HF. Thus, the failing heart of patients with T2D has preserved its ability to sequester lipid without impeding the myocardial contractile function or causing clinically significant acute lipotoxicity in patients with T2D and HF.

Study Limitations

Plasma glucose was increased during high FFA. It can be argued that this might cause a minor increase in myocardial glucose uptake because of a glucose mass effect. However, this seems unlikely because FFA differed >20-fold between the study arms and circulating FFA levels correlate inversely with myocardial glucose uptake.\(^{36}\) Similarly, ketones differed between the study arms, but to our knowledge, no human experiments support that this should affect our results.

Winhofer et al\(^{24}\) report that hyperglycemic clamp and hyperinsulinemia cause an increase in MyLC in normal subjects. We found that MyLC was lowest during hyperinsulinemic-euglycemic clamping (low FFA). We suggest that this discrepancy is because of the large differences in triglycerides and FFA levels between our study arms.

The effect of high lipid levels on insulin sensitivity and hyperinsulinemia was not investigated but could have been addressed in a third study arm by combining high FFA levels with hyperinsulinemic-euglycemic clamp. Further, the applied method to lower FFA levels does not allow us to discriminate between the effects of hyperinsulinemia and suppressed circulating FFA levels. However, a previous study showed no effect on myocardial contractile function in HF patients because of short-term insulin infusion.\(^7\) Although no patients had T2D in this study and thus should be extrapolated with caution, it suggests that the minor changes observed on S′max in the present study were unlikely caused by differences in insulin levels. Whether the applied interventions affected myocardial perfusion is unsettled and needs to be addressed in future studies.

Ideally myocardial perfusion of the septum should have been investigated at screening. However, by history, all patients completing the MRS investigations on both visits were known either to have undergone coronary artery bypass graft or percutaneous coronary intervention for revascularization to the vessels supplying the septum or to have no coronary artery disease by previous coronary angiography. Furthermore, we observed an increase in septal strain during exercise, appearance of microbubbles in the septum of all patients both pre and post exercise, and no angina during the cardiopulmonary exercise test.

The possibility of type 2 statistical errors must be considered. However, we used a crossover design and sensitive, reproducible cardiopulmonary, echocardiographic, and MR spectroscopic techniques with paired measurements.

No female participants were included in the present study and most patients were in New York Heart Association class 2. Whether females or patients in New York Heart Association 3 or 4 would have responded differently is unknown.

Conclusion

The failing heart of patients with T2D can adapt to extreme short-term increases in circulating lipids and does not display features of acute myocardial lipotoxicity. The long-term cardiac effects of modulating myocardial lipid uptake and content await further studies.

Acknowledgments

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Disclosures

Dr. Schär is employed by Philips. The other authors report no conflict.

References

annular velocity measured with Doppler tissue imaging in patients with chronic heart failure caused by left ventricular systolic dysfunction. *Heart*. 2006;92:775–779.


18. van Bilsen M, van Nieuwenhoven F, van der Vusse GJ. Metabolic re-


28. Iozzo P. Seeing is believing: dietary fatty acids hurry up from the stom-


**CLINICAL PERSPECTIVE**

This clinical study addresses the cardiovascular effects of manipulating circulating lipid levels and myocardial lipid content in patients with type 2 diabetes mellitus and heart failure. Thus, it contributes to the understanding of cardiac lipotoxicity and the clinical approach toward patients with type 2 diabetes mellitus and heart failure. Our study shows that myocardial lipid content is inversely correlated with left ventricular ejection fraction and displays much flexibility in response to changes in circulating triglycerides, free fatty acids, and insulin levels. However, short-term suppression of circulating lipid levels and myocardial lipid content has no beneficial effect on the failing diabetic myocardium. However, we observed that this may even have adverse effects with regard to cardiac contractile function. For the practicing clinician, the present study, therefore, shows that reduction of myocardial lipid content through brief suppression in circulating lipids is without beneficial clinical effects in patients with heart failure and type 2 diabetes mellitus. These are new findings in this large subgroup of heart failure patients with a poor prognosis.
Failing Heart of Patients With Type 2 Diabetes Mellitus Can Adapt to Extreme Short-term Increases in Circulating Lipids and Does Not Display Features of Acute Myocardial Lipotoxicity

Roni Nielsen, Helene Nørrrelund, Ulla Kampmann, Won Yong Kim, Steffen Ringgaard, Michael Schär, Niels Møller, Hans Erik Bøtker and Henrik Wiggers

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