The Failing Heart of Patients with Type 2 Diabetes Can Adapt to Extreme Short-Term Increases in Circulating Lipids and Does Not Display Features of Acute Myocardial Lipotoxicity

Nielsen et al: Lipids, Heart Failure and Type 2 Diabetes

Roni Nielsen, MD¹; Helene Nørrelund, MD, PhD, DMSc²; Ulla Kampmann, MD, PhD³;
Won Yong Kim, MD, PhD, DMSc, Prof.¹,⁴; Steffen Ringgaard, MSc, PhD, Ass. Prof.⁴;
Michael Schär, MSc, PhD⁵; Niels Møller, MD, PhD, DMSc, Prof.³;
Hans Erik Bøtker, MD, PhD, DMSc, Prof.¹; Henrik Wiggers, MD, PhD, DMSc, Ass. Prof.¹

¹Dept. of Cardiology, Aarhus University Hospital, Aarhus, Denmark
²Dept. of Medicine, Viborg Hospital, Viborg, Denmark
³Dept. of Endocrinology and Metabolism, Arhus University Hospital, Aarhus, Denmark
⁴The MR Center, Aarhus University Hospital, Aarhus, Denmark
⁵Philips Healthcare, Cleveland, OH, USA

Correspondence to
Roni Nielsen, MD
Department of Cardiology
Aarhus University Hospital, Skejby
8200 Aarhus N, Denmark
Telephone +4578452255
Fax +4578452260
E-mail, roni.r.nielsen@gmail.com

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Abstract

Background—Circulating lipid levels and myocardial lipid content (MyLC) is increased in type 2 diabetes (T2D). This may cause a state of lipotoxicity that compromises left ventricular function and aggravate heart failure. We investigated the relationship between circulating lipid levels, MyLC, and cardiac function together with the acute cardiac effects of high as opposed to low circulating free fatty acid (FFA) and triglyceride (TG) levels in patients with T2D and heart failure.

Methods and Results—Eighteen patients underwent 8-hour intralipid/heparin-infusion (high-FFA) and hyperinsulinemic-euglycemic clamping (low-FFA) in a randomized cross-over-designed study. We applied advanced echocardiography, cardiopulmonary exercise, and MR imaging. MyLC correlated positively with circulating TG (r=0.47, r²=0.22, p=0.003) and FFA (r=0.45, r²=0.20, p=0.001) levels and inversely with left ventricular ejection fraction (LVEF) (r=-0.54, r²=0.29, p=0.004). Circulating FFA concentrations differed between study arms (0.05±0.04mmol/L (low-FFA) vs 1.04±0.27mmol/L (high-FFA), p<0.001) and MyLC increased from 0.78±0.59% (low-FFA) to 1.16±0.73% (high-FFA) (p<0.01). Resting LVEF and global strain did not differ between high- and low-FFA, whereas resting systolic mitral plane velocity (S’max) was highest during high-FFA (3.6±0.8cm/s (low-FFA) vs. 3.8±0.7cm/s (high-FFA), p=0.02). Peak exercise capacity and oxygen consumption did not differ between the study arms, and neither did post exercise measurements of LVEF, global strain, and S’max.

Conclusions—Our findings indicate that the failing heart of patients with T2D can adapt to short-term extreme changes in circulating substrates and does not display features of acute myocardial lipotoxicity.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01192373.

Key Words: left ventricular function, magnetic resonance spectroscopy, heart failure, contrast echocardiography
The myocardium of patients with type 2 diabetes (T2D) loses its metabolic flexibility due to elevated circulating free fatty acids (FFA) levels and myocardial lipid content (MyLC). This creates a state of lipotoxicity that compromises the 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.

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 manipulation 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 randomized cross-over-designed trial. They underwent 8 hours of intralipid/heparin infusion (high-FFA) and hyperinsulinemic-euglycemic clamping (low-FFA). We used advanced echocardiography, cardiopulmonary exercise testing, and magnetic resonance imaging (MRI) to measure cardiovascular function and MR-proton-spectroscopy (MRS) to quantify MyLC.
Methods

Patients

We included 20 non-insulin-treated Caucasian male patients with T2D and chronic HF. The patients were stable on optimal HF medication, in New York Heart Association (NYHA) class 2-3 and had a LVEF ≤45% assessed by echocardiography. We excluded patients with high age (>85 years), cardiac valve disease, physical or psychological disability, creatinine >220 mM, 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 visualised by echocardiography.

Design

All patients were investigated in a randomized cross-over-designed trial on two different occasions 1-6 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 mM using 0.8 mU insulin/kg/min. (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/hour combined with 250 U/hour of heparin (high-FFA). To avoid bias from other antidiabetics, we chose to instruct all participants to pause oral antidiabetic medication 2 days before the investigations. Patients were admitted at 7.45 a.m. and venous cannulas were inserted into each of the upper extremities for infusion and blood sampling. Infusions were initiated at 8.15 a.m. (t=0 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% glucose infusion to avoid hypoglycemia. In the high-FFA arm, isotonic saline was co-administered
with intralipid/heparin infusion and plasma glucose was measured every second hour. On both occasions, blood samples for analysis were drawn again at t=6 hours, echocardiography was performed at t=7 hours, cardiopulmonary exercise testing at t=8 hours, and myocardial MRI followed by MRS of the heart between t=9 and t=10 hours. We were unable to repeatedly perform plasma glucose measurements in the MR scanner room. Thus, the hyperinsulinemic-euglycemic clamp was terminated before the MR investigations for safety reasons. The intralipid/heparin infusion was continued until completion of the MR investigations.

Post-processing of the data was blinded to the investigators.

**Blood samples**

Plasma glucose measurements were performed using HemoCue® Glucose 201 (Ängelholm, 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 samples were analyzed for levels of FFA, insulin, C-peptide, glucagon, cortisol, growth hormone (GH), insulin-like growth factor 1 (IGF-1), and adiponectin as previously described. Adrenaline and noradrenaline were measured by a valid in-house time-resolved high-performance liquid chromatography method, beta-hydroxybutyrate by a commercial amperometric method (Randoxanalysis kit RB1007, Abbott), and N-terminal pro-brain natriuretic peptide (NT-proBNP) using a commercial electrochemiluminescent assay (Roche Diagnostics, Denmark).

**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, Initiios Medical AB, Copenhagen, Denmark) was administered intravenously as previously 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’s method. Peak systolic longitudinal mitral plane velocities during ejection phase (S’max) were measured by tissue Doppler imaging and global strain by 2D speckle tracking as previously described. Measurements were performed at rest and immediately after peak exercise. We assessed left ventricular diastolic function from mitral inflow and tissue Doppler: E/A-ratio, E-deceleration time, isovolumetric relaxation time (IVRT), and mitral plane e’ (early diastolic) velocity. Parameters were estimated as averages of either three (sinus rhythm) or five (atrial fibrillation) consecutive heart beats. All echocardiographic investigations were blinded prior to analysis.

**Resting hemodynamics**

Systolic and diastolic blood pressure was measured in the same arm on both visits, and mean arterial pressure (MAP) was calculated (MAP = (pulse pressure / 3) + diastolic blood pressure).

**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 watts/min. Blood pressure, heart rate, and ECG were measured repeatedly every second minute. Oxygen consumption and carbon dioxide excretion were measured continuously at rest and during the exercise test as described by the manufacturer.
Magnetic resonance investigation

A Philips 1.5 Tesla scanner and a five-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 (4x2x1 cm) was placed to cover the interventricular septum avoiding epicardial lipid deposits and the blood pool. A TR of 3000 ms and a TE of 26 ms were used. We performed 64 water-suppressed acquisitions followed by 16 non-water-suppressed acquisitions and ended the MRS by another 64 water-suppressed acquisitions to measure both lipid and water content of the ROI. MRS data were post-processed using jMRUI version 3.0 to measure the “area under the curve” at 1.3 ppm in the water-suppressed data (intracellular lipid of the ROI) and at 4.7 ppm in the non-water-suppressed data (total water of the ROI). MyLC was calculated as percentage of water content as previously described.9

Outcomes

Primary endpoints were defined as changes in MyLC. Secondary endpoints were changes in LVEF, myocardial contractile function (S’max and global strain), peak exercise capacity, oxygen consumption, post-exercise 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 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±standard deviation (SD). P-values <0.05 were considered significant. Paired t-test or Wilcoxon signed rank test were used to analyze data between study arms. Spearman was used to test for correlations. Two way ANOVA analysis with repeated measurements and Robust clustered variance analysis were used when stated. Confidence intervals (CI) of 95% are presented when appropriate. Based on prior studies, a cross-over 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%. Applying these parameters and complete data sets on at least ten 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. The project is registered at http://www.clinicaltrial.gov identifier NCT01192373.

Results
Patients (Table 1, Figure 1)
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 suffered from 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 post-exercise echocardiography on both occasions. Patients were 67±7 year of age, had an LVEF of 35±8% and were in NYHA class 2 or 3. The HF symptoms were either due to 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 four patients on dietary treatment. Twelve patients completed the MRI and ten patients completed cardiac MRS on both occasions. Drop-outs from the MR analysis were either due to 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 one patient was subjected to angiography within the past three years (7 (5-13) months, median (25-75%)) which included or documented full revascularization of the arteries supplying the septum. The last patient underwent coronary angiography five years before enrollment and was diagnosed with DCM.

**Substrates and hormones**

FFA levels differed more than twenty-fold (0.05±0.04 (low-FFA) vs. 1.04±0.27 mmol/L (high-FFA), p<0.001) and triglycerides approx. four-fold (1.0±0.8 (low-FFA) vs. 3.9±2.0 mmol/L (high-FFA), p<0.001) between the study arms. Insulin levels were lowest during high-FFA (521±244 (low-FFA) vs. 66±35 pmol/L (high-FFA), p<0.001), and plasma glucose levels were highest during high-FFA (5.7±0.5 (low-FFA) vs. 9.4±4.8 mmol/L (high-FFA), p<0.01). C-peptide (p<0.001), glucagon (p<0.001), GH (p<0.01), and ketones (p<0.001) were significantly higher in the high-FFA arm than in the low-FFA arm (data not shown). IGF-1 (p=0.34), cortisol (p=0.82), noradrenalin
(p=0.29), adrenalin (p=0.27), and NT-proBNP (p=0.29) did not differ between the study arms (data not shown). All patients had fasting plasma glucose ≥7 mmol/L. Weight (91±12.3 kg (low-FFA) vs 90.5±12.9 kg (high-FFA), p=0.09), intravenous volume infused (899±333 ml (low-FFA) vs 761±150 ml (high-FFA), p=0.06), and plasma volume calculated as previously described did not differ significantly between the study arms (p=0.09) before the investigations.

MR spectroscopy (Figures 2-4)
MyLC differed by 50% between the study arms (0.78±0.59% vs 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 two correlation did not differ (p=0.08). We identified an outlier with regard to the triglyceride levels by Grubb’s 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 (HOMA) index, C-peptide, glucose, HbA1c, BMI, age, and NT-proBNP levels did not correlate with MyLC (data not shown).

Left ventricular function, contractility and resting hemodynamics (Table 2)
No differences between the study arms were observed in LVEF (ΔLVEF=1±6%, CI: -4% to 2%, p=0.60 (echocardiography); ΔLVEF=1±4%, CI: -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.
Exercise test, hemodynamics, and post-exercise echocardiography (Table 2)

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 (RER) was significantly higher during rest and peak exercise in the high-FFA arm than in the low-FFA arm. Due to the placement of the ROI during MRS, we measured regional septal strain from rest to exercise and found it to increase (p=0.02, two-way ANOVA with repeated measurements).

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 have 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. 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 neutral or even potentially detrimental effects of suppression in circulating FFA levels on left ventricular function and cardiac efficiency. These discordant results may reflect differences in the pathophysiology of patients with and without diabetes and differences in the severity of the metabolic derangement such patients undergo. The FFA levels
differed more than 20-fold and triglyceride levels four-fold between the study arms. Even so, we
detected no significant deterioration in our endpoints 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 due to the fact that S’max is more
reproducible\textsuperscript{19} and more sensitive to subtle contractile changes than LVEF, even by contrast-
enhanced echocardiography.\textsuperscript{6} Furthermore, the present changes in S’max may have clinical
relevance as it has been shown to be an independent predictor of mortality.\textsuperscript{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,\textsuperscript{21} but the
opposite was observed. Even though weight and plasma volume did not differ significantly between
the study arms, more fluid tended to be infused during low-FFA (approx. 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.\textsuperscript{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 \(e’\).\textsuperscript{23} However, this was
not observed. Our finding seems not to be explained by a confounding effect of insulin stimulation
on the sympathetic nervous system\textsuperscript{24} since 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 supports that GH or glucagon,\textsuperscript{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.\textsuperscript{26} C-peptide differed between the study arms, but increased C-peptide
levels have no vascular effects during preserved endogenous C-peptide production.\textsuperscript{27} Since 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 and coworkers, who reported that both glucose and FFA oxidation are required for optimal function of the failing heart in non-T2D HF patients. Thus, this previous study and the present observations indicate that increased myocardial FFA metabolism in stable HF patients does not decrease LVEF, but on the contrary it increases stroke volume and S’ max. A potential explanation of this observation may be that in terms of ATP yield, thus, the decrease in cardiac fatty acid oxidation during low circulating lipid levels is not compensated for by the increase in glucose oxidation. Whether the discrepancies between Tuunanen et al. and the present findings are rooted in differences with regard to T2D and the applied interventions are unknown. However, further studies are required to elucidate whether the failing heart responds differently to more modest reductions in circulating lipids, as previously stated. Although the changes in circulating substrates were extreme in our study, the clinical significance of decreased S’ max during hyperinsulinemic-euglycemic clamping and increased contractile function during hyperglycemia and elevated FFA as previously shown 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. MyLC measured in myocardial biopsies is also elevated in patients with reduced LVEF due to aortic stenosis and end-stage dilated cardiomyopathy, and it is even more elevated in case of coexisting T2D. Although we were unable to detect differences in LVEF and exercise capacity between high and low circulating lipids, as previously stated.

While the changes in circulating substrates were extreme in our study, the clinical significance of decreased S’ max during hyperinsulinemic-euglycemic clamping and increased contractile function during hyperglycemia and elevated FFA as previously shown could suggest that a major decrease in lipid load may be detrimental in patients with T2D and HF.
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, it may give rise to decreased energy metabolism and accumulation of toxic lipid intermediates, 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 or even greater 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.

FFA, triglyceride levels and MyLC correlated positively. In contrast, a previous study showed that MyLC did not increase due to elevated triglycerides 4 hours after oral lipid intake in normal test subjects. However, recently it was shown that in patients with impaired glucose tolerance as compared to healthy test subjects postprandial myocardial lipid uptake is increased even though FFA levels decrease while triglyceride levels increase. 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 due to a glucose mass effect. However, this seems unlikely since FFA differed more than 20 fold between the study arms and circulating FFA levels correlate inversely with myocardial glucose uptake. Similarly, ketones differed between the study arms, but to our knowledge, no human experiments support that this should affect our results.

Winhofer et al. 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 due to the large differences in triglycerides and FFA levels between our study arms.

The effect of high lipid levels on insulin sensitivity as well as hyperinsulinemia was not investigated, but could have been addressed in a 3rd 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 due to short-term insulin infusion. Even though 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 CABG and/or PCI 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 NYHA class 2. Whether females or patients in NYHA 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.

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Disclosures

Michael Schär is employed by Philips. The remaining authors have no conflict of interest.

References


Table 1. Patient Characteristics

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Medication / treatment

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Table 2. Echocardiographic, hemodynamic and cardiopulmonary exercise parameters

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Post exercise</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low FFA N=18</td>
<td>High FFA N=18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>P-value</td>
</tr>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>38±7</td>
<td>38±10</td>
<td>0.61</td>
</tr>
<tr>
<td>S’ max (cm/s)</td>
<td>3.6±0.8</td>
<td>3.8±0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Strain (%)</td>
<td>-11.1±2.5</td>
<td>-11.3±2.7</td>
<td>0.45</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.0±1.3</td>
<td>5.1±1.2</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-velocity (m/s)</td>
<td>0.73±0.23</td>
<td>0.72±0.25</td>
<td>0.44</td>
</tr>
<tr>
<td>E-deceleration time (ms)</td>
<td>264±112</td>
<td>258±111</td>
<td>0.75</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>20±9</td>
<td>19±9</td>
<td>0.46</td>
</tr>
<tr>
<td>E/A ratio*</td>
<td>1.2(0.8-2.2)</td>
<td>1.1(0.7-2.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>97±37</td>
<td>102±14</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87±14</td>
<td>92±11</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>62±12</td>
<td>65±13</td>
<td>0.08</td>
</tr>
<tr>
<td>RER</td>
<td>1.00±0.07</td>
<td>0.86±0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise capacity (W)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>O2 used (ml/min/kg)</td>
<td>3.5±0.9</td>
<td>3.5±1.1</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Bold highlights parameters that differ significantly between study arms. (LVEF: Left Ventricular Ejection Fraction, IVRT: Isovolumetric relaxation time, MAP: Mean Arterial Pressure, NA: Not Available, 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).
**Figure Legends**

Figure 1. CONSORT diagram.

Figure 2. Myocardial lipid content (MyLC) expressed as percentage of water content measured by MRS. MyLC differed significantly between the study arms (*: 0.006) (black dots: low FFA; white squares: high FFA).

Figure 3. Correlation of LVEF and MyLC illustrating a negative association between LVEF and MyLC (black dots: low FFA; white squares: high FFA).

Figure 4. The association between MyLC, FFA, triglycerides and insulin levels. (black dots: low FFA; white squares: high FFA).
Assessed for eligibility (n=43)

Excluded (n=23):
- not meeting inclusion criteria (n=21)
- meeting exclusion criteria (n=2)

Randomized (n=20)

Allocated to:
- Low FFA at 1st visit and high FFA at 2nd visit (n=10)
- High FFA at 1st visit and low FFA at 2nd visit (n=10)

Lost to follow-up (n=1)
- withdrew consent prior to 1st visit
- cardiac arrest prior to 1st visit

Analyzed (n=9)
- echocardiography pre/post exercise (n=9)
- exercise test (n=9)
- myocardial MRI (n=7)
- MR-spectroscopy (cardiac) (n=6)

Analyzed (n=9)
- echocardiography pre/post exercise (n=9)
- exercise test (n=9)
- myocardial MRI (n=5)
- MR-spectroscopy (cardiac) (n=4)
MyLC and LVEF

$r = -0.54$, $r^2 = 0.40$, $p = 0.004$
The Failing Heart of Patients with Type 2 Diabetes Can Adapt to Extreme Short-Term Increases in Circulating Lipids and Does Not Display Features of Acute Myocardial Lipotoxicity

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

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