Increased myocardial lipid content (MYCL) recently has been linked to the development of cardiomyopathy in diabetes. In contrast to steatosis in skeletal muscle and liver, previous investigations could not confirm a link between MYCL and insulin resistance. Thus, we hypothesized that cardiac steatosis might develop against the background of the metabolic environment typical for prediabetes and early type 2 diabetes: combined hyperglycemia and hyperinsulinemia. Therefore, we aimed to prove the principle that acute hyperglycemia (during a 6-h clamp) affects MYCL and function (assessed by 1H magnetic resonance spectroscopy and imaging) in healthy subjects (female subjects: n = 8, male subjects: n = 10; aged 28 ± 5 years; BMI 22.4 ± 2.6 kg/m²). Combined hyperglycemia (202.0 ± 10.6 mg/dL) and hyperinsulinemia (110.6 ± 59.0 µU/mL) were, despite insulin-mediated suppression of free fatty acids, associated with a 34.4% increase in MYCL and a decrease in FFAs) (13). The rise in plasma FFA concentrations secondary to caloric restriction causes an increase in the curve of insulin (R = 0.59, P = 0.0009) and a decrease in end-systolic volume (P = 0.0002) during the clamp. Furthermore, an increase in ejection fraction (P < 0.0001) and a decrease in diastolic function in normal subjects (11). Thus, cardiac steatosis might develop against the background of the metabolic environment typical for patients with prediabetes or early type 2 diabetes: hyperglycemia, hyperinsulinemia, and elevated plasma concentrations of free fatty acids (FFAs).

Although a clear relationship between insulin resistance and increased ectopic intracellular lipid content in skeletal muscle and liver has been demonstrated (8–10), we recently could not observe an association between insulin resistance and myocardial lipid accumulation in normoglycemic subjects (11). Thus, cardiac steatosis might develop against the background of the metabolic environment typical for patients with prediabetes or early type 2 diabetes: hyperglycemia, hyperinsulinemia, and elevated plasma concentrations of free fatty acids (FFAs). Pronounced hyperglycemia, secondary to short-term deprivation of insulin dosage in patients with type 1 diabetes, did not affect MYCL (12). However, recent data suggest that elevated plasma FFAs directly affect myocardial lipid deposition in the presence of low insulin concentrations. Elevation of plasma FFA concentrations during physical exercise is associated with an increase in MYCL and a rise in ejection fraction (EF); these effects can be suppressed by the administration of glucose (and thus a decrease in FFAs) (13). The rise in plasma FFA concentrations secondary to caloric restriction causes an increase in MYCL and a decrease in diastolic function in healthy subjects (14), as well as in patients with type 2 diabetes (15), which can be blunted by suppression of FFA release by pharmacological inhibition of lipolysis. Both studies confirm the short-term flexibility of the myocardial triglyceride pool in healthy subjects and in patients with diabetes. Taken together, excessive FFA supply, secondary to unrestrained lipolysis in the presence of decreased insulin concentrations, likely exceeds myocardial oxidation capacity and leads to the accumulation of unoxidized lipids and lipid intermediates in the cytosol.

However, elevation of plasma FFAs by a high-fat, high-energy diet for 3 days did not increase MYCL but did increase hepatic lipid content (16), suggesting that short-term meal studies preferentially target liver metabolism. It is of note that only plasma insulin, but not glucose concentrations, was increased. Thus, the available data on the potential direct effects of plasma FFAs on MYCL are inconsistent and do not sufficiently explain cardiac steatosis in patients with impaired glucose tolerance or type 2 diabetes (1,2,7).
Given that (postprandial) hyperglycemia and hyperinsulinemia are central and early features of metabolic diseases, we hypothesized that combined hyperglycemia and hyperinsulinemia induce myocardial lipid accumulation.

We previously have shown that insulin infusion in patients with type 2 diabetes leads to lipid accumulation in liver and skeletal muscle, likely resulting from insulin-mediated inhibition of lipolysis and lipid oxidation, stimulation of intracellular triglyceride synthesis, and/or increased uptake of circulating FFAs (17). The resulting competition of glucose and fatty acids for mitochondrial oxidation further decreases myocardial fatty acid utilization (18,19). Reduced fatty acid oxidation, together with insulin-stimulated FFA uptake and triglyceride synthesis, results in net lipid storage. However, whether hyperglycemia and consequent hyperinsulinemia might also affect lipid accumulation in the heart currently is unknown. Therefore, the objective of this study was to investigate the impact of acute hyperglycemia and consequent hyperinsulinemia on MYCL and function in healthy subjects.

RESEARCH DESIGN AND METHODS

Healthy men and women were recruited to participate in this study. Exclusion criteria included the presence of any acute or chronic inflammatory diseases, arterial hypertension, evidence of coronary artery disease, and history of inflammatory diseases, as well as the tendency toward claustraphobia and the existence of metal devices or other magnetic material in or on the subjects. A baseline examination was performed including a complete medical history, physical examination, and blood sampling for electrolytes, kidney, and liver function, as well as blood count to determine subject eligibility. Subjects were included when eligibility criteria were fulfilled and after giving written, informed consent. The protocol was approved by the human ethics committee of the Medical University of Vienna. No subject was taking any medication regularly.

All examinations were performed at the Metabolic Laboratory of the Division of Endocrinology and Metabolism, Department of Internal Medicine III, and the MR-Centre of Excellence, Department of Radiodiagnoses, both at the Medical University of Vienna. Subjects were asked to refrain from vigorous physical activity and to ingest an isocaloric diet (30 kcal/kg/day: carbohydrate/protein/fat: 55/15/30%) for 3 days prior to the experiments. Female subjects were instructed to refrain from physical activity and to ingest an isocaloric diet (30 kcal/kg/day: carbohydrate/protein/fat: 55/15/30%) for 3 days prior to the experiments. Female subjects included when eligibility criteria were fulfilled and after giving written, informed consent. The protocol was approved by the human ethics committee of the Medical University of Vienna. No subject was taking any medication regularly.

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RESULTS

Eighteen healthy subjects (10 male and 8 female) met the inclusion criteria and underwent the study protocol (Table 1). Men and women were matched for age (male subjects: 27.6 ± 3.4 years, female subjects: 29.0 ± 7.2 years, P = 0.02), body mass index (male subjects: 25.3 ± 2.6 kg/m², female subjects: 21.4 ± 2.3 kg/m², P = 0.9). Metabolic changes. As expected, standardized hyperglycemia (mean glucose: 202.0 ± 10.6 mg/dL) caused an increase in plasma insulin and C-peptide concentrations. The pronounced suppression of circulating FFAs was mediated by hyperinsulinemia (all P < 0.0001) (Fig. 2). In addition, a comparable increase in MYCL (baseline: 0.20 ± 0.17%, clamp: 0.26 ± 0.22%, P = 0.0003) was observed in both male (baseline: 0.22 ± 0.22%, clamp: 0.29 ± 0.29%, P = 0.01) and female (baseline: 0.18 ± 0.09%, clamp: 0.25 ± 0.1%, P < 0.02) subjects (Fig. 3).

Changes in cardiac function parameters. The assessment of myocardial function at baseline, as well as during the sixth hour of the hyperglycemic-hyperinsulinemic clamp,
revealed an increase in EF and median end-systolic wall thickness, as well as a significant decrease in ESV (see Table 2). The E/A ratio, a parameter of diastolic function, remained unchanged during the experiment.

**Correlation analyses.** The increase in MYCL (ΔMYCL) was positively correlated with the AUC of plasma insulin and C-peptide concentrations (Fig. 4), whereas no association was found between ΔMYCL and changes in cardiac function parameters. When these variables were integrated into a linear model, the AUC of C-peptide remained predictive for ΔMYCL. No correlation was observed between insulin sensitivity and MYCL (at baseline and during the sixth hour of the clamp) or ΔMYCL.

The rise in insulin concentrations during the clamp was positively correlated with ΔEF (Fig. 5A) and inversely associated with the change in ESV (Spearman analysis) (Fig. 5B). The association between ΔEF and Δinsulin remained significant in regression analyses, even after adjustment for heart rate.

Additional interesting associations observed were the inverse correlation between septal wall thickness (at the sixth hour of the clamp test) and the AUC of FFAs ($R = -0.63, P < 0.007$) and a tendency toward an inverse

| TABLE 1 Baseline characteristics of study participants | Means ± SD |
|-------------------------------------------------------|------------|
| n (female/male)                                       | 8/10       |
| Age (years)                                           | 28.3 ± 5.3 |
| BMI (kg/m²)                                           | 22.4 ± 2.6 |
| Body surface area (m²)                                | 1.87 ± 0.26|
| M/I ratio [(mg/kg/min)/(µU/mL)]                       | 0.19 ± 0.08|
The current study provides evidence that combined hyperglycemia and hyperinsulinemia induce myocardial lipid accumulation in normal subjects, despite insulin-mediated suppression of plasma FFAs. We also show that the increase in insulin concentrations during sustained hyperglycemia is tightly associated with the increase in MYCL and acute changes in cardiac functional parameters: $\Delta$EF ($R = -0.04$, $P = 0.86$), $\Delta$ESV ($R = 0.02$, $P = 0.93$), and $\Delta$cardiac output ($R = -0.3$, $P = 0.24$).

DISCUSSION
The current study provides evidence that combined hyperglycemia and hyperinsulinemia induce myocardial lipid accumulation in normal subjects, despite insulin-mediated suppression of plasma FFAs. We also show that the increase in insulin concentrations during sustained hyperglycemia is tightly associated with the increase in MYCL and acute changes in cardiac function (EF and ESV).
It has been convincingly shown that elevation of plasma FFAs is associated with an increase in MYCL (13–15). The underlying mechanism is thought to be an overstrain of the cellular FFA oxidation machinery, which results in accumulation of toxic lipid by-products in the cytosol. Here, we show that even in the presence of suppressed circulating FFAs, combined hyperglycemia and hyperinsulinemia are able to induce myocardial lipid accumulation in normal subjects. The tight association between the increase in MYCL and the extent of glucose-induced insulin release indicates that insulin is the key mediator. This conclusion is supported by a previous study, which showed that hypoglycemia in the presence of low insulin concentrations (attributed to deprivation of insulin dosage) does not affect MYCL in patients with type 1 diabetes (12).

The rise in MYCL could have resulted from 1) an increased uptake of circulating FFAs, 2) an insulin-mediated stimulation of intracellular triglyceride synthesis, and/or 3) an insulin-mediated inhibition of lipolysis and lipid oxidation.

Exposure to insulin in vitro leads to increased uptake and esterification of FFAs, whereas triglyceride hydrolysis and FFA oxidation are reduced in the rodent soleus muscle (29). We previously have shown that insulin infusion, designed to achieve normoglycemia in patients with type 2 diabetes, stimulates lipid accumulation in skeletal muscle and liver (17).

Inhibition of lipid oxidation, as a result of substrate competition between fatty acids and glucose for mitochondrial oxidation (Randle cycle) (18,19), likely contributed to the observed effects. Fatty acids and glucose, the two main substrates of myocardial metabolism, reach the cytosol via transporters, mainly CD36 and GLUT4 (30), respectively. In the presence of hyperglycemia and consequent hyperinsulinemia, insulin forcefully stimulates myocardial glucose uptake via increased GLUT4 translocation to the cellular membrane, thereby fostering substrate competition between fatty acids and glucose. The resulting switch in mitochondrial substrate utilization from fatty acids to glucose is mediated mainly by malonyl-CoA. Malonyl-CoA derives from acetyl-CoA (via carboxylation by acetyl-CoA carboxylase 2) and inhibits carnitine palmitoyltransferase I (19), which controls the rate-limiting step of mitochondrial FFA uptake and, in turn, oxidation. Of note, insulin was reported to be able to directly stimulate acetyl-CoA carboxylase activity and, thus, to suppress mitochondrial lipid oxidation (31). Reduced fatty acid oxidation may result in accumulation of unoxidized lipid intermediates in the cytosol, leading to lipid storage and cardiac steatosis.

We previously have shown that MYCL, in contrast to ectopic lipid accumulation in skeletal muscle and liver, does not relate to systemic insulin resistance in normoglycemic subjects (11). In line with these results, we did not observe any relationship between MYCL and insulin sensitivity (M/I ratio) in the current study of rather insulin-sensitive

| Parameters of myocardial function and lipid content at baseline and during the 6th hour of sustained hyperglycemia and hyperinsulinemia | Baseline | Clamp (6th hour) | ΔValues | P |
|---|---|---|---|---|
| Heart rate (bpm) | 62.7 ± 10.4 | 64.4 ± 5.8 | 1.7 ± 9.8 | NS |
| EF (%) | 62.3 ± 4.4 | 67.7 ± 5.5 | 5.5 ± 3.8 | <0.0001 |
| End diastolic volume (mL/m²) | 78.3 ± 12.8 | 74.9 ± 14.5 | -3.4 ± 7.8 | NS |
| ESV (mL/m²) | 29.9 ± 7.0 | 24.7 ± 7.9 | -5.2 ± 4.7 | 0.0002 |
| Stroke volume (mL/m²) | 48.5 ± 6.8 | 50.2 ± 8.2 | 1.8 ± 5.2 | NS |
| Cardiac index (L/min/m²) | 3.0 ± 0.5 | 3.2 ± 0.6 | 0.2 ± 0.7 | NS |
| Myocardial mass (g/m²) | 69.5 ± 13.4 | 68.2 ± 12.3 | -1.4 ± 5.2 | NS |
| Median wall thickness at ES (mm) | 11.1 ± 2.1 | 12.1 ± 2.4 | 0.9 ± 0.8 | 0.0008 |
| Median wall thickness at ED (mm) | 7.1 ± 1.3 | 7.1 ± 1.4 | 0.03 ± 0.7 | NS |
| E/A ratio | 2.0 ± 0.5 | 1.9 ± 0.4 | -0.09 ± 0.3 | NS |
| MYCL* | 0.20 ± 0.17 | 0.26 ± 0.22 | 0.06 ± 0.06 | 0.0009 |

ΔValues describe quantitative changes, and P values represent the statistical significance between the two time points. *Presented in the percentage of water reference signal. ED, end-diastolic; ES, end-systolic.

FIG. 4. Correlations between the increase in MYCL (ΔMYCL) and the AUCs of insulin (A) and C-peptide (B) during the clamp.
subjects. This is in contrast to our previous study on the effects of insulin infusion on skeletal muscle lipid content in patients with type 2 diabetes, where intramyocellular lipid content correlated positively with insulin sensitivity after prolonged insulin infusion.

Because women with overt diabetes were reported to display increased cardiac steatosis compared with their male counterparts (7), and sex differences in myocardial blood flow and fatty acid metabolism recently were described (32), we aimed to investigate whether acute changes in MYCL also might be more pronounced in women. In our study, basal MYCL, as well as the change in MYCL, did not differ between male and female participants; therefore, no sex-specific differences in acute myocardial lipid accumulation were observed.

As expected, changes in cardiac function parameters in response to acute glucose-induced hyperinsulinemia were recorded: EF and end-systolic left ventricular wall thickness were increased compared with baseline. In addition, a reduction in ESV was observed. The rise of EF was positively correlated with the increase in insulin concentrations during the clamp, as well as inversely associated with the suppression of FFA concentrations. This is in accordance with previous findings that high-dose insulin infusion increases cardiac output as a result of improving systolic cardiac function (33). Insulin is known to be a stimulator of the sympathetic nervous system (34), which might have contributed to the observed effects. Nevertheless, even when adjusted for heart rate, the change in EF remained significantly related to the changes in insulin concentrations during the clamp. The correlation between the rise in insulin concentrations and the changes in ESV and EF also remained significant after adjustment for the infused volume, indicating that insulin mediated the observed effects on systolic cardiac function. In addition, because FFA oxidation requires more oxygen than glucose utilization, the observed rise in EF could be explained by improved cardiac performance attributed to increased glucose oxidation, as suggested by the observed inverse association between the rise in EF and the suppression of plasma FFA concentrations. However, it cannot be excluded that the observed acute improvements in myocardial function may, in the presence of chronic insulin oversupply in patients with metabolic diseases, result in maladaptive changes and, thus, myocardial dysfunction.

Our study did not address the question of whether myocardial steatosis, per se, alters myocardial function. Based on current evidence and our results, we assume that increased MYCL highlights a state of disturbed myocardial substrate metabolism. Recent findings in Wistar rats showed that both a high-fat and a high-fat/high-carbohydrate (Western) diet lead to a similar gain in body weight; however, only the Western diet induced cardiac contractile dysfunction, which was associated with a decreased palmitoleoyl-CoA content and a decreased unsaturated-to-saturated fatty acids ratio in the myocardium. The disturbances in MYCL/composition were traced back to altered hepatic de novo lipogenesis (35). This indicates that in addition to impaired myocardial lipid metabolism, quantitatively and qualitatively altered hepatic lipid synthesis might contribute to myocardial lipid storage and, consequently, dysfunction. In addition, we agree with these authors that lipotoxicity should be replaced by the term glucolipotoxicity (36) when talking about the cardiometabolic complications in patients with obesity and diabetes.

Some limitations must be considered. The MR methods used in the current study did not allow us to discern the precise alterations in myocardial fuel physiology underlying the observed rise in MYCL. Because biopsies of the human myocardium are not feasible in a research setting, investigations on human myocardial metabolism are limited to noninvasive techniques. Advanced high-field MRS has the potential to facilitate the measurement of qualitative changes in MYCL by allowing the monitoring of the degree of saturation of myocardial lipids (37). However, to our knowledge, these methods have not yet been applied on the beating human myocardium. In addition, positron emission tomography has been used to measure myocardial fatty acid utilization, oxidation, and esterification using radioactively labeled fatty acids. Hence, future studies might combine MR imaging/MRS and positron emission tomography to elucidate the exact mechanisms underlying our current observations.

In summary, insulin release in response to hyperglycemia induces a short-term increase in MYCL in healthy subjects. This effect was observed even in the presence of insulin-mediated suppression of plasma FFA concentrations. These findings support the hypothesis that postprandial and/or chronic hyperinsulinemia and hyperglycemia in prediabetes and early type 2 diabetes enhance myocardial steatosis and might thereby contribute to the development of heart failure.
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Y.W. researched data and wrote the manuscript. M.Krš., C.-H.A., and G.R. researched data, contributed to the discussion, and reviewed the manuscript. D.J. and A.H. researched data. S.T. and A.L. contributed to the discussion and reviewed the manuscript. M.Kre. researched data, contributed to the discussion, reviewed the manuscript, and was also the supervisor of the project. M.Kre. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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