A high-fat diet increases adiposity but maintains mitochondrial oxidative enzymes without affecting development of heart failure with pressure overload

David J. Chess,1,2 Ramzi J. Khairallah,1 Karen M. O’Shea,1,3 Wenhong Xu,1 and William C. Stanley1,2,3

1Division of Cardiology, Department of Medicine, University of Maryland, Baltimore, Maryland; and 2Department of Physiology and Biophysics and 3Department of Nutrition, School of Medicine, Case Western Reserve University, Cleveland, Ohio

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A high-fat diet increases adiposity but maintains mitochondrial oxidative enzymes without affecting development of heart failure with pressure overload. Am J Physiol Heart Circ Physiol 297: H1585–H1593, 2009. First published September 18, 2009; doi:10.1152/ajpheart.00599.2009.—A high-fat diet can increase adiposity, leptin secretion, and plasma fatty acid concentration. In hypertension, this scenario may accelerate cardiac hypertrophy and development of heart failure but could be protective by activating peroxisome proliferator-activated receptors and expression of mitochondrial oxidative enzymes. We assessed the effects of a high-fat diet on the development of left ventricular hypertrophy, remodeling, contractile dysfunction, and the activity of mitochondrial oxidative enzymes. Mice (n = 10–12/group) underwent transverse aortic constriction (TAC) or sham surgery and were fed either a low-fat diet (10% of energy intake as fat) or a high-fat diet (45% fat) for 6 wk. The high-fat diet increased adipose tissue mass and plasma leptin and insulin. Left ventricular mass and chamber size were unaffected by diet in sham animals. TAC increased left ventricular mass (~70%) and end-systolic and end-diastolic areas (~100% and ~45%, respectively) to the same extent in both dietary groups. The high-fat diet increased plasma free fatty acid concentration and prevented the decline in the activity of the mitochondrial enzymes medium chain acyl-coenzyme A dehydrogenase (MCAD) and citrate synthase that was observed with TAC animals on a low-fat diet. In conclusion, a high-fat diet did not worsen cardiac hypertrophy or left ventricular chamber enlargement despite increases in fat mass and insulin and leptin concentrations. Furthermore, a high-fat diet preserved MCAD and citrate synthase activities during pressure overload, suggesting that it may help maintain mitochondrial oxidative capacity in failing myocardium.

fatty acids; mitochondria; obesity

DIETS WITH A HIGH RELATIVE fat content are commonly used for weight loss and maintenance; however, little is known about the effects of fat intake on the development and progression of heart failure. Patients with hypertension and subsequent left ventricular (LV) hypertrophy frequently develop heart failure (19). Recent observations suggest that this process may be either adversely or favorably affected by dietary fat intake (5, 30). Dietary fat affects cardiac gene expression, structure, metabolism, and contractile function through changes in plasma lipids and hormones (39). Long-chain fatty acid oxidation supplies most of the metabolic fuel for the healthy heart but is reduced in heart failure due to decreased expression and activity of fatty acid oxidation enzymes (39). Genetic rat and mouse models of increased cardiac fatty acid uptake have greater cardiac triglyceride accumulation, LV chamber enlargement, and contractile dysfunction (1). In our models of chronic pressure overload, we have found that an extremely high-fat diet (60% of energy intake from fat) either attenuated (9, 25, 26, 36, 37) or did not affect (4) the development of LV chamber enlargement and heart failure compared with a standard low-fat diet.

Animals consuming a low-fat diet respond to pressure overload with a decrease in the activity of mitochondrial enzymes involved in fatty acid oxidation, which may be prevented by high fat intake (3, 6). Long-chain fatty acids activate peroxisome proliferator-activated receptor-α, which increases the expression of key enzymes of lipid oxidation (15). We observed that a high-fat diet in the absence of obesity prevented the decline in the activity of the fatty acid β-oxidation enzyme medium chain acyl-coenzyme A dehydrogenase (MCAD) in rat and mouse models of pressure overload-induced LV hypertrophy and heart failure (4, 26). Heart failure decreases mitochondrial oxidative capacity in skeletal muscle (22), and in the absence of obesity, a high-fat diet increases the activity and expression of mitochondrial enzymes in skeletal muscle of normal rats (13). Thus a high-fat diet may also improve skeletal muscle mitochondrial oxidative capacity in heart failure.

Although these findings suggest that a high-fat diet may be optimal for preventing LV remodeling and myocardial contractile and metabolic dysfunction in hypertension, these data were obtained in the absence of any difference in body mass between dietary treatments. An increase in adipose mass is a major confounding variable when assessing the effects of a high-fat diet on the heart, since it can elevate secretion of leptin from adipocytes, which exerts proinflammatory effects in a variety of tissues (21) and can trigger hypertrophy in isolated myocytes (16). Recent studies in normotensive mice found that long-term consumption of a high-fat diet (45% of energy intake) did not adversely affect cardiac function when energy intake was restricted to prevent an increase in fat mass (10). When high-fat chow was provided ad libitum, an increase in
adipose stores ensued with either no evidence for cardiac pathology (42) or moderate cardiac dysfunction (10). Obesity can increase circulating C-reactive protein (CRP) and decrease the anti-inflammatory adipokine adiponectin (7, 8), thereby accelerating cardiac dysfunction and ventricular remodeling (27). Thus, in the setting of chronic hypertension, an increase in fat mass induced by a high-fat diet could worsen the development and progression of heart failure via stimulation of inflammatory processes and leptin-induced cardiac growth. At present, experimental evidence for this concept is lacking.

The purpose of the present study was to determine whether an increase in adipose tissue mass induced by a moderately high-fat diet (45% of energy from fat) would accelerate the development of cardiac hypertrophy and heart failure in response to severe pressure overload. This diet was selected because it is similar to the relative fat intake seen in commonly prescribed human diets and because it increases adipose mass and serum leptin in mice (10). We hypothesized that the high-fat diet would increase adipose tissue mass and circulating leptin, insulin, and CRP, decrease plasma adiponectin, and accelerate LV hypertrophy and heart failure under conditions of severe pressure overload. Studies were performed in the well-established mouse model of pressure overload induced by transverse aortic constriction (TAC) (3, 4, 6). Animals were fed either a standard low-fat/high-carbohydrate diet (10% of energy from fat, 70% from starch) or a moderately high-fat diet (45% of energy from fat, 35% from starch). We assessed the effects of diet and TAC on LV mass and chamber size, serum leptin and insulin, the mRNA expression and activity of mitochondrial enzymes, and molecular markers of heart failure [atrial natriuretic factor (ANF) and myosin heavy chain-β (MHC-β)]. We also measured markers of inflammation, specifically circulating levels of CRP and adiponectin and cardiac mRNA levels for the inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6). Since heart failure decreases mitochondrial oxidative capacity in skeletal muscle (22) and a high-fat diet can upregulate oxidative capacity (13), we also assessed the effects of TAC and diet on the activity of skeletal muscle mitochondrial enzymes.

METHODS

Study design. The goal of this study was to assess the effects of a high-fat diet that increases body weight and adipose tissue mass on the development of LV hypertrophy and heart failure in mice subjected to severe chronic pressure overload. Previously, we demonstrated that mice subjected to moderate severity TAC (banded using a 26-gauge needle) and fed a cocoa butter-derived high-fat diet (60% fat) composed of saturated fatty acids (mainly stearate and palmitate) did not become obese and had a similar degree of LV hypertrophy, chamber enlargement, and contractile dysfunction as mice fed a standard low-fat/high-carbohydrate diet (10% fat) (4). Thus, in the present study, we subjected animals to more severe TAC (27-gauge needle) and fed a high-fat diet (45% fat) high in monounsaturated fatty acids (mainly oleate) to induce a greater increase in adipose and body mass (10, 42). One day following TAC or sham surgery, mice were assigned to dietary treatment and maintained for 6 wk. Each surgical and/or dietary treatment group had 10–12 animals at onset. After 6 wk of treatment, LV dimensions were assessed by echocardiography, followed 1–3 days later by a terminal surgery to harvest tissue and collect plasma and serum samples. All analyses were performed with the investigators blinded to treatment. This study was conducted according to the Guidelines for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, Revised 1996) and was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Maryland at Baltimore.

Induction of pressure overload. TAC was performed on male C57BL/6J mice (aged 10 wk, 28–32 g) as described previously using a 27-gauge needle (6, 14, 18). The sham procedure was identical without aortic ligation. Animals were maintained on a reverse 12-h:12-h light-dark cycle.

Diet. All diets were custom formulated by Research Diets (New Brunswick, NJ) and were matched for micronutrient content. As a percentage of the total energy, the low-fat diet contained 70% carbohydrate (58% energy from cornstarch and 12% from maltodextrin) and 10% fat (7% lard and 3% soybean oil). The high-fat diet derived 45% energy from fat (42% lard and 3% soybean oil) and 35% from cornstarch. The fat in the chow was composed mostly of oleate and palmitate (19% and 11% of total energy in the chow, respectively), with relatively little stearate (6%). All diets contained 20% protein from casein 1 + l-cystine. Animals were fed a standard commercial rodent chow (Harlan Teklad 2243, Global 14% Protein Rodent Maintenance Diet) for at least 1 wk before surgery. One day following surgery, mice were assigned randomly to either the low-fat or high-fat diet. Food and water were provided ad libitum for the remaining 6 wk of the study.

Echocardiography. Echocardiographic measurements of LV size and function were performed under isoflurane anesthesia at 6 wk postsurgery using a VisualSonics Vevo 770 In Vivo Imaging System (Toronto, Ontario, Canada) as previously described (6, 18). LV end-diastolic area (EDA) and end-systolic area (ESA) were planimetered from long-axis cine loops and used to calculate area of fractional shortening (aFS) using the equation aFS = [(EDA – ESA)/EDA] × 100%. Analyses were performed with the investigator blinded to surgical and dietary treatment.

Blood pressure measurements. Systolic blood pressure was measured at 3 wk postsurgery using a Hatters Instruments SC1000 Dual-Channel Blood Pressure Analysis System (Cary, NC). Animals were subjected to analysis on 3 consecutive days, each analysis consisting of a 5-min preliminary acclimation phase followed by 10 min of data recording. Systolic blood pressure was recorded each minute for the 10-min period. Reported values are means ± SE for all values obtained over the 3 consecutive days.

Terminal surgery. After 6 wk of treatment, animals were subjected to terminal surgery in the fed state between 3 and 6 h after initiation of the dark phase. Mice were weighed and anesthetized with 1.5–2.0% isoflurane. The thoracic cavity was opened and the heart was removed, and the LV was dissected, weighed, freeze-clamped, and stored at −80°C. Pooled blood was collected from the thoracic cavity and separated into serum and plasma. Epididymal, retroperitoneal, and subcutaneous fat was removed and weighed.

Metabolic measurements. Plasma concentrations of glucose, free fatty acids, triglycerides, insulin, and adiponectin along with serum leptin and tissue triglycerides were measured as previously described (3, 4). Glucose and insulin were measured in blood samples collected after a 12-h fast as well as in blood collected during the terminal surgery when animals were in the fed state. Plasma CRP was measured using a commercial ELISA kit (Alpco Diagnostics). The tissue activities of MCAD, citrate synthase, and glucose 6-phosphate dehydrogenase (G6PDH) were measured spectrophotometrically as previously described (6). Succinate dehydrogenase (SDH) activity was measured according to the assay described by St Pierre and Boutillier (38).

mRNA expression analysis. RNA isolation and cDNA synthesis were performed as described previously (3). The expression of atrial natriuretic factor (Nppa), myosin heavy chain-α (Myh6) and -β (Myh7), TNF-α, IL-6, MCAD, citrate synthase, NADPH oxidase 4 (NOX4), and peptidylpropyl isomerase a (ppia, internal control) was assessed using the following Applied Biosystems TaqMan Gene Expression Assays: Mm01255747_g1 (Nppa), Mm00440354_m1 (Myh6), Mm00600555_m1 (Myh7), Mm00443258_m1 (Tnf), Mm99999064_m1 (Il6), Mm00431611_m1 (Acadm), Mm00466043_m1 (Cs), Mm00479239_g1 (AJP-Heart Circ Physiol • VOL 297 • NOVEMBER 2009 • www.ajpheart.org).
Table 1. Gravimetric data obtained during the terminal surgery following 6 wk of dietary treatment

<table>
<thead>
<tr>
<th></th>
<th>Sham Low Fat</th>
<th>TAC Low Fat</th>
<th>Sham High Fat</th>
<th>TAC High Fat</th>
<th>TAC vs. Sham</th>
<th>Low vs. High Fat</th>
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<tr>
<td>n</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>11</td>
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<tr>
<td>Terminal body mass, g</td>
<td>36.4±2.3</td>
<td>30.5±1.8*</td>
<td>40.1±2.4</td>
<td>36.2±2.5†</td>
<td>—</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Epididymal fat mass, mg</td>
<td>952±258</td>
<td>444±110</td>
<td>1,539±263</td>
<td>1,397±314</td>
<td>—</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Retroperitoneal fat mass, mg</td>
<td>311±79</td>
<td>145±44</td>
<td>592±98</td>
<td>516±116</td>
<td>—</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Subcutaneous fat mass, mg</td>
<td>481±83</td>
<td>269±63</td>
<td>810±159</td>
<td>710±173</td>
<td>—</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Total fat mass, mg</td>
<td>1,744±411</td>
<td>858±215*</td>
<td>2,940±503</td>
<td>2,623±595†</td>
<td>—</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Left ventricular mass, mg</td>
<td>116±5</td>
<td>195±7</td>
<td>118±5</td>
<td>185±16</td>
<td>P &lt; 0.05</td>
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</tr>
<tr>
<td>Tibial length, mm</td>
<td>19.9±0.2</td>
<td>19.4±0.3</td>
<td>20.2±0.1</td>
<td>19.7±0.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Right ventricular mass/tibial length, mg/mm</td>
<td>1.44±0.13</td>
<td>1.62±0.16</td>
<td>1.54±0.08</td>
<td>1.86±0.20</td>
<td>P &lt; 0.05</td>
<td>—</td>
</tr>
<tr>
<td>Total atrial mass/tibial length, mg/mm</td>
<td>0.52±0.06</td>
<td>1.56±0.39</td>
<td>0.52±0.05</td>
<td>1.17±0.25</td>
<td>P &lt; 0.05</td>
<td>—</td>
</tr>
<tr>
<td>Total heart mass/tibial length, mg/mm</td>
<td>7.81±0.40</td>
<td>13.22±0.81</td>
<td>7.92±0.31</td>
<td>12.41±1.19</td>
<td>P &lt; 0.05</td>
<td>—</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>0.1±0.2</td>
<td>19.7±0.2</td>
<td>0.3±2</td>
<td>107±6</td>
<td>—</td>
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</tr>
</tbody>
</table>

Values are means ± SE. TAC, transverse aortic constriction. The TAC vs. sham column represents significant main effects of surgery. The low vs. high fat column represents significant main effects of diet. *P < 0.05 compared with respective sham; †P < 0.05 compared with low-fat-fed TAC group.

No significant differences were observed between surgical and/or dietary treatment groups.

Body and fat masses. There were no significant differences in body mass at the time of surgery, but the terminal body mass was significantly greater in both the sham and TAC high-fat-fed animals (Table 1). Mice fed the high-fat diet had an increase in the mass of retroperitoneal, epididymal, and subcutaneous fat (Table 1) and a greater sum of fat masses both in absolute terms and when expressed as a percentage of body mass (Fig. 1A) compared with the low-fat diet in both sham and TAC groups. TAC decreased the mass of each fat depot and total fat mass in low-fat-fed animals. No differences were observed between sham and TAC in the high-fat-fed animals.

Metabolites and hormones. Fasting plasma glucose and insulin were unchanged by surgical or dietary treatment (Table 2). As a main effect, high-fat feeding significantly increased insulin concentration in the fed state (Table 2). The insulin level in the low-fat-fed TAC group was significantly less than the high-fat-fed TAC group (Table 2). Plasma glucose concentration in the fed state was unchanged by surgical or dietary treatment.
Serum leptin was increased by high-fat compared with low-fat feeding independent of surgical treatment (Fig. 1B) and was positively correlated with the sum of the retroperitoneal, epididymal, and subcutaneous fat masses ($r = 0.96; P < 0.01$). Leptin has been shown to activate AMPK (23), which can suppress protein synthesis and hypertrophy in isolated cardiomyocytes (2). Therefore, we assessed AMPK activation in the myocardium (Fig. 2). There were no differences in total or

<table>
<thead>
<tr>
<th>Metabolite or Hormone</th>
<th>Low Fat</th>
<th>High Fat</th>
<th>TAC vs. Sham</th>
<th>Low vs. High Fat</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Fasting plasma glucose, mM</td>
<td>4.34±0.34</td>
<td>3.59±0.68</td>
<td>4.35±0.20</td>
<td>5.25±0.37</td>
</tr>
<tr>
<td>Fed plasma glucose, mM</td>
<td>5.24±0.22</td>
<td>5.82±0.35</td>
<td>5.11±0.17</td>
<td>5.41±0.66</td>
</tr>
<tr>
<td>Plasma free fatty acids, mM</td>
<td>0.24±0.05</td>
<td>0.22±0.02</td>
<td>0.32±0.02</td>
<td>0.34±0.02†</td>
</tr>
<tr>
<td>Plasma triglycerides, mg/ml</td>
<td>70.1±17.1</td>
<td>74.3±13.7</td>
<td>59.0±6.2</td>
<td>50.0±5.0</td>
</tr>
<tr>
<td>Cardiac triglyceride, μmol·mg ww$^{-1}$</td>
<td>4.08±0.31</td>
<td>3.34±0.62</td>
<td>4.11±0.40</td>
<td>3.28±0.32</td>
</tr>
<tr>
<td>Skeletal muscle triglyceride, μmol·mg ww$^{-1}$</td>
<td>21.8±2.4</td>
<td>11.1±1.8*</td>
<td>29.3±2.4</td>
<td>31.0±3.6†</td>
</tr>
<tr>
<td>Liver triglyceride, μmol·mg ww$^{-1}$</td>
<td>11.1±2.1</td>
<td>6.34±1.57</td>
<td>10.9±1.9</td>
<td>14.0±3.1</td>
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<tr>
<td>Plasma adiponectin, μg/ml</td>
<td>1.81±0.19</td>
<td>1.93±0.13</td>
<td>1.85±0.13</td>
<td>2.03±0.21</td>
</tr>
<tr>
<td>Fasting plasma insulin</td>
<td>0.18±0.05</td>
<td>0.09±0.03</td>
<td>0.24±0.07</td>
<td>0.25±0.07</td>
</tr>
<tr>
<td>Fed plasma insulin</td>
<td>0.13±0.02</td>
<td>0.11±0.02</td>
<td>0.19±0.05</td>
<td>0.25±0.05†</td>
</tr>
<tr>
<td>Plasma C-reactive protein, ng/ml</td>
<td>11.5±0.6</td>
<td>11.6±0.3</td>
<td>11.7±0.3</td>
<td>10.9±0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. The TAC vs. sham column represents significant main effects of surgery. The low vs. high fat column represents significant main effects of diet. *$P < 0.05$ compared with respective sham; †$P < 0.05$ compared with low-fat-fed TAC group.

Fig. 2. Representative blots and quantified densitometry for phosphorylated (A) and total (B) AMP-activated protein kinase (AMPK) protein levels in left ventricular (LV) tissue after 6 wk of treatment. Labels above gel lanes designate the following: LFS, low-fat sham; LFT, low-fat TAC; HFS, high-fat sham; HFT, high-fat TAC. C: phosphorylation relative to total protein. Differences and interactions between surgical and dietary groups were assessed by 2-way ANOVA. Data are means ± SE. *$P < 0.05$ compared with respective sham. AU, arbitrary units.
phosphorylated AMPK protein levels among groups (Fig. 2B). However, the ratio of phosphorylated to total protein was significantly decreased by TAC compared with sham (Fig. 2C). High-fat feeding increased plasma free fatty acid concentration as a main effect (Table 2). Within TAC groups, the high-fat diet produced significantly greater free fatty acid concentration compared with the low-fat diet.

**Tissue triglyceride content.** Plasma, cardiac, and liver triglyceride concentrations were unchanged by surgical or dietary treatment (Table 2). Within skeletal muscle, triglyceride concentration was significantly increased by high-fat feeding as a main effect. Low-fat-fed TAC animals had significantly lower skeletal muscle triglyceride concentration compared with their respective sham and high-fat-fed TAC animals (Table 2).

**Blood pressure.** No differences in systolic blood pressure were observed at 3 wk regardless of surgical or dietary treatment (Table 1).

**Heart mass.** TAC increased the mass of the total heart, left ventricle, and atria in both low-fat- and high-fat-fed animals (Table 1 and Fig. 3A). Right ventricular mass was unchanged by surgical or dietary treatment (Table 1). There were no significant dietary effects within either the sham or TAC groups.

**LV dimensions and molecular markers of heart failure.** TAC increased LV EDA and ESA compared with sham in both the low- and high-fat-fed animals (Fig. 3, B and C). aFS was decreased comparably by TAC in low- and high-fat-fed TAC groups compared with sham (Fig. 3D). Dietary treatment had no significant effects on LV dimensions. TAC increased the mRNA expression of ANF, MHC-β, and NOX4 in low- and high-fat-fed mice compared with sham (Fig. 5). No change was observed in MHC-α expression regardless of surgical or dietary treatment.

**Metabolic enzymes.** TAC decreased the activities of MCAD and citrate synthase in the low-fat-fed animals compared with sham, but this effect was prevented in the animals fed the high-fat diet (Fig. 4). Furthermore, the MCAD-to-citrate synthase activity ratio was increased significantly in high- compared with low-fat-fed TAC animals (Table 3), suggesting selective upregulation of fatty acid oxidation in the high-fat TAC group. Sham animals showed no increase in MCAD or citrate synthase activity with high-fat feeding (Fig. 4, A and C), consistent with our previous findings (4, 24, 26). Cardiac mRNA expression of MCAD was not affected by surgical or dietary treatment. Citrate synthase mRNA expression was increased by high- compared with low-fat feeding as a main effect.
effect (Fig. 5). TAC also reduced the activity of SDH compared with sham animals regardless of dietary treatment (Table 3). There was a trend for the high-fat diet to prevent this depressed SDH activity compared with low-fat-fed animals, but this effect did not reach statistical significance ($P < 0.067$).

Heart failure upregulates G6PDH, which under pathological conditions may fuel superoxide production by NADPH oxidases and cardiac superoxide levels and increase oxidative damage (6, 11, 12, 35). The activity of G6PDH was increased by TAC in both the low- and the high-fat group compared with sham with no significant effect of dietary treatment (Table 3).

Heart failure decreases mitochondrial oxidative capacity in skeletal muscle in rats and humans (22); however, the effects of TAC-induced heart failure on skeletal muscle mitochondrial oxidative enzymes have not been reported. It was recently observed that a high-fat diet in the absence of obesity increases mitochondrial enzymes in skeletal muscle in rats (13). Therefore, we investigated potential changes in the activity of mitochondrial enzymes in the soleus muscle. TAC significantly decreased the activity of MCAD in both dietary groups. The high-fat diet increased MCAD activity in both sham and TAC groups (Fig. 4D). There were no significant differences in skeletal muscle citrate synthase (Fig. 4B) or SDH (Table 3) activity among groups. There was no effect of surgery or diet on the MCAD to citrate synthase ratio, suggesting that the high-fat diet did not upregulate the capacity for fatty acid oxidation in skeletal muscle.

Inflammatory markers. TAC increased mRNA expression of IL-6 in both the low- and high-fat-fed groups compared with sham (Fig. 5). However, mRNA levels for TNF-α were unaffected by TAC or diet. Plasma CRP and adiponectin were also not different among treatment groups (Table 2).
Table 3. Enzyme activities in the left ventricular myocardium and soleus after 6 wk of dietary treatment

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Low Fat</th>
<th>High Fat</th>
<th>TAC vs. Sham</th>
<th>Low vs. High Fat</th>
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<tr>
<td></td>
<td>Sham</td>
<td>TAC</td>
<td>Sham</td>
<td>TAC</td>
</tr>
<tr>
<td>Myocardial G6PDH, μmol·gww⁻¹·min⁻¹</td>
<td>0.203±0.015</td>
<td>0.161±0.010</td>
<td>0.225±0.014</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Myocardial MCAD:CS</td>
<td>0.171±0.006</td>
<td>0.169±0.003</td>
<td>0.182±0.005*</td>
<td>—</td>
</tr>
<tr>
<td>Myocardial SDH, μmol·gww⁻¹·min⁻¹</td>
<td>3.20±0.07</td>
<td>3.09±0.23</td>
<td>2.40±0.18</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Soleus MCAD:CS</td>
<td>0.036±0.001</td>
<td>0.039±0.001</td>
<td>0.037±0.001</td>
<td>—</td>
</tr>
<tr>
<td>Soleus SDH, μmol·gww⁻¹·min⁻¹</td>
<td>1.42±0.12</td>
<td>1.44±0.09</td>
<td>1.50±0.06</td>
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</table>

Values are means ± SE. The TAC vs. sham column represents significant main effects of surgery. The low vs. high fat column represents significant main effects of diet. *P < 0.05 compared with low-fat-fed TAC group. G6PDH, glucose 6-phosphate dehydrogenase; MCAD, medium chain acyl-coenzyme A dehydrogenase; CS, citrate synthase; SDH, succinate dehydrogenase.

DISCUSSION

The novel finding of the present study is that there is a similar degree of LV hypertrophy, remodeling, and contractile dysfunction in response to severe pressure overload in mice fed a high-fat diet despite displaying characteristics of the metabolic syndrome (e.g., increased adiposity and elevated circulating leptin, insulin, and free fatty acids) compared with mice fed a standard low-fat diet. In addition, treatment with a high-fat diet prevented one of the hallmarks of LV hypertrophy and heart failure: a decrease in the activity of mitochondrial oxidative enzymes, which may help preserve cardiac energetics and slow deterioration of contractile function under conditions of chronic pressure overload. Taken together, these findings support the concept that a high-fat diet per se does not accelerate LV hypertrophy and development of heart failure in chronic hypertension.

Our results are in contrast with our previous work in rats with salt-induced hypertension or aortic banding, which found prevention of LV chamber enlargement and improved survival with a high-fat diet (60% of energy intake) compared with a standard low-fat diet (9, 25, 26, 37). Previous studies also demonstrated that mice subjected to less severe pressure overload we saw a decrease in both myocardial MCAD-to-citrate synthase ratio was decreased by 10.220.33.6 on July 16, 2017 http://ajpheart.physiology.org/ Downloaded from by high-fat feeding. *P < 0.05 compared with low-fat feeding.

Fig. 5. mRNA expression of selected genes measured by semiquantitative RT-PCR. Expression was normalized to cyclophilin A, an internal control, which did not change with surgical or dietary treatment, and the mean of the low-fat-fed sham group (dashed line). Left: atrial natriuretic factor (ANF), myosin heavy chain-α (MHC-α), and myosin heavy chain-β (MHC-β). Right: tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), MCAD, and citrate synthase (CS). Data are means ± SE. *P < 0.05 compared with respective sham. Brackets indicate a significant main effect of high- compared with low-fat feeding.
feeding (4). Moreover, we observed an increase in the MCAD-to-citrate synthase ratio in TAC animals on the high-fat diet compared with the low-fat-fed TAC group, suggesting that a high-fat diet has a greater effect on the capacity for fatty acid oxidation than on the capacity for citric acid cycle activity under conditions of pressure overload.

The results of the present investigation and our studies in rats (9, 25, 26, 36, 37) and mice (4) contrast sharply with the recent report by Raher et al. (30), which showed that feeding a high-fat diet to C57BL/6J mice with TAC increased LV mass and chamber volume, contractile dysfunction, and mortality compared with TAC mice on a low-fat diet. As in the present study, Raher et al. banded using a 27-gauge needle; however, they used a diet composed of 60% of energy from fat (mainly lard) and studied the animals for 28 days postsurgery. They did not observe an increase in body mass but found elevated insulin and glucose levels with impaired glucose tolerance. These differences suggest that the response to a 60% fat diet composed of lard may trigger a cardiometabolic syndrome that is more severe than what is achieved with a 45% fat diet. In our previous study, in TAC mice with a 60% fat diet composed mainly of saturated fat from cocoa butter, we reported similar hypertrophy and LV dysfunction after TAC compared with a low-fat diet. Raher et al. (30) attributed the contrasting results of the two studies to differences in the fatty acid profile between lard and cocoa butter. However, our results presented herein suggest that the differences may be due to an extremely high intake of lard. Furthermore, we initiated the high-fat diet immediately after surgery in 10-wk-old animals, whereas Raher et al. (30) fed the high-fat diet to 7-wk-old mice for 9 days before surgery, perhaps resulting in a more adverse cardiac response to TAC than with our protocol.

Dietary fat intake can affect fat deposition and adipose endocrine function. In the present study, mice fed the high-fat diet had significantly greater fat mass, which correlated strongly with serum leptin concentration. Studies in human and rodent cardiomyocytes show that leptin can directly stimulate hypertrophy and increase reactive oxygen species generation (16, 20, 31, 32, 41). On the other hand, complete leptin deficiency is associated with myocardial lipid accumulation and cardiac pathology (40). Clearly leptin can exert both cardioprotective and harmful effects on the heart, as has been reviewed extensively (1, 16, 17, 29, 33, 34). The impact of elevated leptin on the heart likely depends on the duration of exposure, the degree of hyperleptinemia, and any concomitant changes in related hormones (e.g., insulin and adiponectin). Nonetheless, in the current study, we demonstrated that high-fat feeding significantly increased whole body adiposity and circulating leptin without deleterious effects on the heart. We did not observe a decrease in serum adiponectin concentration, consistent with the previous observation that there are not lower adiponectin levels until 20 wk on a high-fat diet (28). This suggests that the increase in adipose mass was insufficient to suppress adiponectin secretion. Additional studies are required with a more prolonged and severe diet-induced increase in adipose mass to clarify the role of alterations in adipokines in the development and progression of heart failure.

Markers of inflammation were measured to determine whether dietary macronutrient composition has an effect on the inflammatory response to aortic banding. There was no change in plasma CRP (Table 1) or mRNA expression of TNF-α. Expression of IL-6 was upregulated with TAC compared with sham, suggesting that inflammatory mediators are regulated differentially in the development of hypertrophy and contractile dysfunction. A dietary effect on IL-6 expression was not observed, suggesting that cornstarch or the fatty acids within the lard-based Western diet were not sufficient to modify inflammation.

In conclusion, this study demonstrates that a high-fat diet that increases adiposity and serum leptin does not worsen cardiac hypertrophy or contractile dysfunction in response to pressure overload. Furthermore, treatment with a high-fat diet preserved the activities of mitochondrial enzymes compared with low-fat-fed animals, implying a beneficial effect of high-fat diets on the stressed myocardium. Further studies are needed to determine whether chronic consumption of high fat can maintain normal mitochondrial function and slow the progression of heart failure.

GRANTS

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DISCLOSURES

No conflicts of interest are declared by the authors.

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