Cardiovascular Function in a Rat Model of Diet-Induced Obesity

Joan F. Carroll, Woineshet J. Zenebe, Taylor B. Strange

Abstract—The obesity-prone/obesity-resistant rat model has been used to study mechanisms responsible for obesity-related abnormalities in renal function and blood pressure, but whether this model exhibits cardiac dysfunction has not been determined. We tested the hypothesis that obesity-prone rats would display cardiovascular abnormalities seen in other diet-induced obese models (ie, hypertension, tachycardia, left ventricular hypertrophy, increased collagen deposition, reduced cardiac contractility, and increased end diastolic pressure). Male Sprague-Dawley rats were fed a control diet or a moderate fat diet containing 32% kcal as fat while hemodynamics were continuously monitored using telemetry. After 12 weeks, obesity-prone rats were significantly heavier and had greater body fat compared with obesity-resistant rats and controls, but daily (20 hours/d) averages and diurnal rhythms of blood pressure and heart rate did not differ among groups. Echocardiographic indices of cardiac structure and function, histological evidence of cardiac collagen, and directly measured heart weights did not differ among groups. Peak left ventricular pressure, end diastolic pressure, +dP/dt, and −dP/dt were also not significantly different among groups. Plasma cholesterol and hepatic cholesterol were significantly higher in obesity-prone rats compared with obesity-resistant rats and controls; hepatic triglycerides were higher in obesity-prone rats compared with controls (P≤0.05). Leptin was significantly higher in obesity-prone rats compared with controls and across all groups was significantly correlated with body fat (P≤0.05). These results suggest that 12 weeks of a moderate fat diet in the obesity-prone/obesity-resistant rat model induced lipid and endocrine abnormalities typical of obesity but was not sufficient to cause significant cardiac abnormalities. (Hypertension. 2006;48:65-72.)

Key Words: hypertrophy ■ echocardiography ■ blood pressure ■ cardiac output ■ rats ■ diurnal rhythm

The prevalence of obesity in the United States has increased in the last several decades, with two-thirds of Americans now considered overweight or obese.1,2 Obesity decreases life expectancy and increases the incidence of stroke and coronary heart disease.3 Elucidating mechanisms involved in obesity-related cardiac dysfunction requires use of appropriate animal models. Genetic models of obesity in rodents such as the ob/ob rat, the Zucker obese rat, and the spontaneously hypertensive model that has recently shown promise is the obesity-prone (OP) rat.11–14 In this model, Sprague-Dawley rats are fed a diet containing 32% kcal as fat. Several studies have demonstrated that OP rats exhibit hypertension, hypercholesterolemia, hyperinsulinemia, renin–angiotensin system activation, and increased renal oxidative stress.11,13–15 However, whether cardiac function is altered by obesity in this model has not been determined. Therefore, we tested the hypothesis that OP rats would display cardiovascular abnormalities qualitatively similar to those seen in other diet-induced obese models9,16,17 (ie, hypertension, tachycardia, increased left ventricular [LV] weight, concentric/eccentric hypertrophy, collagen deposition, reduced cardiac contractility, and increased end-diastolic pressure [EDP]). In addition, because the OR group consumed a high-fat diet but did not become obese, we tested whether obesity produced these changes independently of diet composition.

Materials and Methods

Animals

Experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of North Texas Health Science Center. Protocols were carried out according to the Guide for the Care and Use of Laboratory Animals (National Institutes
of Health Publication 86-23, revised 1985) and regulations of the Animal Welfare Act. Male Sprague-Dawley rats (394±4 g, Charles River, Wilmington, Mass) were housed individually in a humidity- and temperature-controlled room with a 12-hour light cycle (0700 hours:1900 hours). Food and water were provided ad libitum.

**Diet Protocol**
After 1-week acclimation, rats were randomly divided into 2 groups: normal fat diet (NFD, n=7) and moderate fat diet (MFD, n=16). The NFD consisted of 11% kcal fat, 73% kcal carbohydrate, and 17% kcal protein. The MFD consisted of 32% kcal fat, 51% kcal carbohydrate, and 17% kcal protein (Research Diets, New Bruns-wick, NJ). Body weight and food intake were measured weekly. After 12 weeks, rats consuming the MFD were ranked based on weight gain, as described previously. Rats on the MFD exhibiting the greatest weight gains were referred to as OP (n=6), whereas those exhibiting the lowest weight gains were referred to as OR (n=5). Rats not falling into OP or OR groups were not used further.

**Hemodynamics**
Before starting the protocol, telemetry transmitters (model PA-C40, Data Sciences International) were aseptically implanted in the abdominal aorta by the vendor. Four-second bursts of blood pressure (BP) and heart rate (HR) were collected every 3 minutes, and a daily average calculated from data collected between 1100 hours and 0700 hours. (Animal care activities occurred between 0700 hours and 1100 hours; these data were excluded from analysis.) Three days of measurements before starting the diet protocol were averaged to provide a control value. Thereafter, weekly averages were calculated. To evaluate diurnal rhythms of HR and BP, the 20-hour period of daily data collection was divided into 4 periods (1100 to 1600 hours, 1600 to 2100 hours, 2100 to 0200 hours, and 0200 to 0700 hours). The night–day value was computed as the difference between the 0200 to 0700-hours and the 1100 to 1600-hours periods. On the day of sacrifice, transmitter drift was determined by comparing telemetry and direct aortic measurements of BP (see below); this value was used to correct BP measurements.

**M-mode Echocardiography**
Rats were anesthetized with isoflurane (1% to 2% with 0.8 L/min O2, administered with a facemask) and placed in a left lateral position. Two-dimensional directed M-mode images were obtained using a Phillips HDI 5000 ultrasound instrument and a 12-MHz phased array transducer. Images were taken in the parasternal long axis plane at the level of the mitral valve leaflets. LV posterior wall thickness (PWT), LV diameter, and septal thickness were taken in both systole and diastole. HR was calculated from the R-R interval. Short axis views of the aorta were used to obtain ejection time (ET) measured from the opening to the closing of the aortic valve. All M-mode parameters were the average of 3 cardiac cycles. After M-mode measurements were made, a pressure transducer (Mikro-tip 3F, model SPR-249, Millar Instruments) was advanced into the LV via the left common carotid artery to obtain EDP, end systolic pressure, LV +dP/dt, and LV –dP/dt. Mean BP was obtained with the catheter tip in the aorta. LV end-diastolic and end-systolic wall stress were calculated from M-mode and pressure data using the formula: wall stress = 0.334×P×LVID/(PWT×[1–PWT/LVID]), where P is LV pressure, and LVID is LV internal diameter using the respective diastolic (d) and systolic (s) measures. Fractional shortening (FS) was calculated as (LVIDd–LVIDs)/LVIDd×100. Rate corrected velocity of circumferential shortening was calculated as FS/(ET×R-R).

**Histology**
A transverse section of heart was immersion-fixed in neutral buffered formalin for 5 to 12 hours at room temperature on a rocker, dehydrated in a series of graded alcohols, cleared in xylene, and embedded in paraffin. Tissue was sectioned (5-μm thick) on a Jung Biocut 2035 microtome, mounted on charged slides, and dried overnight on a slide warmer at 45°C. After deparaffinization in xylene, sections were rehydrated in a series of graded alcohols, rinsed in PBS, and stained for collagen following Gomori’s 1-step trichrome stain or for morphology with hematoxylin and eosin. Under a 10× microscope objective, interstitial collagen volume fraction was determined as the percentage of green-stained connective tissue area per total myocardial area in each microscopic field using a minimum of 15 to 20 randomly selected areas per heart. Under a 40× objective, myofiber cross-sectional area was determined from hematoxylin-eosin–stained sections in ~20 randomly chosen cardiomyocytes per heart. Analyses were performed by a blinded investigator using a Nikon TE2000 inverted microscope and a commercially available analysis system (Image-Pro Plus, Version 5, Media Cybernetics).

**Statistical Analyses**
For diurnal rhythms, group HR and BP values were compared during the control period and week 12 using repeated measures ANOVA. All other variables were analyzed using a 1-way ANOVA and Tukey

### TABLE 1. Characteristics of Experimental Groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obesity-Prone</th>
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</tr>
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<tbody>
<tr>
<td>Body weight at start, g</td>
<td>390.7±6.8</td>
<td>396.5±9.2</td>
<td>374.3±7.9</td>
</tr>
<tr>
<td>Control week BP, mm Hg</td>
<td>101.1±3.4</td>
<td>101.7±1.2</td>
<td>102.9±1.8</td>
</tr>
<tr>
<td>Week 12 BP, mm Hg</td>
<td>111.5±2.3</td>
<td>113.8±2.2</td>
<td>109.1±4.2</td>
</tr>
<tr>
<td>Week 12–control BP, mm Hg</td>
<td>10.5±1.9</td>
<td>12.1±1.9</td>
<td>6.2±3.0</td>
</tr>
<tr>
<td>Control week HR, beats/min</td>
<td>418.3±4.2</td>
<td>411.5±6.5</td>
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</tr>
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<td>Week 12 HR, beats/min</td>
<td>370.6±4.9</td>
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<td>388.5±7.4</td>
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<td>Week 12 HR–control HR, beats/min</td>
<td>−47.7±2.6</td>
<td>−31.7±5.7*</td>
<td>−34.6±4.0</td>
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<tr>
<td>Control week night–day HR, beats/min</td>
<td>48.3±8.6</td>
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<tr>
<td>Week 12 night–day HR, beats/min</td>
<td>60.2±5.7</td>
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<td>Control week night–day BP, mm Hg</td>
<td>7.2±1.8</td>
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<td>Week 12 night–day BP, mm Hg</td>
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Data expressed as mean±SE.

*P<0.05, control>OP.

**Blood and Tissue Analyses**
Insulin, leptin, and ghrelin were analyzed using commercially available radioimmunoassay kits (Linco, Inc). Glucose was measured using a One-Touch Ultra glucometer (Lifescan, Inc). Plasma total cholesterol and triglycerides were determined by respective enzymatic reagents (Data Medical Associates) using a microtiter plate assay. Plasma HDL cholesterol was determined enzymatically after precipitation of apoprotein B-containing lipoproteins (Data Medical Associates). Hepatic lipids were extracted as described by Folch et al. The lipid-containing fraction was dried, re dissolved in etha- nol, and cholesterol and triglycerides were determined as described above.

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*P<0.05, control>OP.
Results

Animal Characteristics and Hemodynamics
There were no significant differences between control, OP, and OR in initial body weight, BP, or HR (Table 1). At sacrifice, OP was heavier ($P<0.002$) and had a greater percent weight gain ($P=0.0001$) compared with controls and OR (Figure 1). Absolute body fat ($P=0.016$) and fat weight normalized for body weight ($P=0.040$) were higher in OP compared with controls. Absolute and normalized fat weight in OR were intermediate between OP and controls ($P>0.05$, Figure 1). Despite greater body weight in OP, mean BP during week 12, the change in BP during 12 weeks (Table 1), and the slope of the body weight/BP relationship across 12 weeks (Figure 2) did not differ among groups ($P>0.05$). Week-12 HR did not differ among groups. However, HR declined across 12 weeks in all groups; the drop in HR was greater in controls compared with OP ($P=0.03$).

Diurnal rhythms of HR and BP during the control period and week 12 are shown in Figure 3. There were significant time×week interactions for HR ($P=0.0001$) and BP ($P=0.002$), indicating that daily pattern of HR and BP differed in week 12 compared with the control period. However, there were no group differences in diurnal rhythms, nor were there any group differences in the night–day BP and HR values (Table 1, $P>0.05$).

Feed Consumption
OP had greater total feed consumption in the 12 weeks compared with OR (2205±119 versus 1836±55 g, respectively, $P=0.02$), but total feed consumption of OP and controls (2063±43) did not differ (Figure 4). Because of the greater caloric density of the MFD, total energy consumption in 12 weeks was higher in OP (40.7±2.2 MJ) compared with both...
OR (33.9±1.0 MJ) and controls (33.7±0.7 MJ) (P=0.005). Weight gain normalized for total energy consumption (ie, feed efficiency) was greater in OP (8.04±0.29 g/MJ) compared with OR (6.84±0.26 g/MJ) and controls (6.69±0.24 g/MJ) (P=0.004).

**Plasma and Tissue Hormones, Glucose, and Lipids**

Plasma total cholesterol (P=0.005) and hepatic cholesterol (P=0.011) were higher in OP compared with OR and controls (Figure 5). Plasma HDL cholesterol (P=0.010) and hepatic triglycerides (P=0.012) were higher in OP compared with controls. Plasma triglycerides did not differ significantly among groups. Leptin was significantly higher in OP compared with controls (Table 2), and plasma leptin was significantly correlated with total body fat (R²=0.23, P=0.07). Ghrelin was not significantly different among groups (Table 2) but tended to be negatively correlated with total body fat (R²=0.23, P=0.07).

**Organ Dimensions**

Absolute liver weights were higher in OP compared with the other groups (P=0.006), but this difference was not significant when normalized for body weight (Table 3). Total kidney weight tended to be higher in OP compared with OR and controls (P=0.056) but normalized kidney weight did not differ among groups. Absolute and normalized heart and hind limb muscle weights were not significantly different among groups.

**Cardiac Structure and Function**

OP had significantly greater systolic PWT compared with OR (P=0.036) and tended to have greater diastolic PWT compared with OR (P=0.10) (Table 4). Chamber diameters measured in diastole and systole were not significantly different among groups. Peak LV pressure, EDP, developed pressure, +dP/dt, −dP/dt, and +dP/dt normalized for aortic mean pressure (+dP/dt/P) were also not significantly different among groups (Table 5).

**Cardiac Histology**

There was a trend for interstitial collagen volume fraction to be greater in OR compared with OP (3.33±0.72 versus 1.60±0.34%, respectively) (P=0.08). Collagen volume fraction in controls was 2.86±0.48%. Myocyte area was not significantly different among groups, with average values of 196±17, 181±17, and 198±25 μm², for lean, OP, and OR, respectively.

**Discussion**

We hypothesized that OP rats would display cardiovascular abnormalities typically seen in other diet-induced obese models (ie, hypertension, tachycardia, increased LV weight, concentric/eccentric hypertrophy, collagen deposition, reduced cardiac contractility, and increased EDP). We found that OP rats demonstrated the expected body weight and body fat gains.
across 12 weeks but did not exhibit hypertension, abnormal
diurnal rhythms of HR and BP, or increased cardiac weight.
Further, echocardiographic indices of cardiac structure and
function and histological evidence of cardiac collagen and
myocyte hypertrophy did not differ among groups. This is in
marked difference to obesity in other animal models and in
humans and suggests that 12 weeks of a MFD in the
OP/OR rat model was not sufficient to cause significant
cardiac abnormalities.

In contrast to earlier studies, BP was not elevated
in OP. We used telemetry to obtain control measurements
of BP and HR measured 20 hour/d, and compiled weekly
averages of BP and HR for 12 weeks. Unexpectedly, there
were only small increases in mean BP in 12 weeks (10.5,
12.1, and 6.2 mm Hg for controls, OP, and OR, respectively)
and no differences among groups during week 12. Even
when systolic BP values were compared, as in earlier stud-
ies, increases averaged 11 to 17 mm Hg, and groups
did not differ during week 12 (134.8±2.7, 137.5±3.3, and
131.2±4.8 mm Hg for controls, OP, and OR, respectively).

Investigations using the tail cuff method to assess BP in
the OP/OR model have found increases in systolic BP of
≈30 mm Hg for OP during the protocol and differences
between controls and OP of ≈25 to 30 mm Hg at the end
of the protocol. However, the tail cuff method may
be susceptible to errors because of handling stress,
but this is by no means universal. Other studies
using telemetry to measure BP in the OP/OR model found
increases in mean and systolic BP during a 9-week protocol of
<5 and 10 mm Hg, respectively. During week 9, mean BP was
significantly greater in OP than in OR, but only by ≈8 mm Hg.
Interestingly, OP and OR did not differ in BP during the first 8
weeks of the 9-week protocol. In another study, BP was
measured using an indwelling arterial catheter, and mean BP
was significantly higher in OP compared with controls and
OR, but only by 8 mm Hg. In studies using telemetry (present
study and in Reference ), BP values represent 20+ hours/d
of data, encompassing both active (dark) and sleep (light)
phases, and BP recording does not involve restraint stress.
Thus, telemetry recordings may better reflect the overall
impact of obesity in this model. Together these data suggest
that when BP is measured chronically rather than acutely the
OP/OR rat model of obesity is not convincingly hypertensive.

The discrepancy in conclusions regarding BP between
the present study and previous studies do not appear to be
because of differences in body weight or fat. A prior 10-week
study found weight gains of 282 and 214 g in OP versus
controls, values that are slightly lower than weight gains in
the present study. Estimated final body weights for OP and
controls were 671 and 600 g, respectively, also slightly lower
than the present results. This may reflect the shorter protocol
(10 versus 12 weeks). In another study, final body weights for
controls and OP were also similar to present values. Total

**Table 2. Plasma Hormones and Glucose in Control, OP, and OR Rats**

<table>
<thead>
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<th>Control</th>
<th>Obesity-Prone</th>
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</tr>
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<tbody>
<tr>
<td>Glucose, mmol/L</td>
<td>12.8±1.9 (6)</td>
<td>18.9±4.6 (5)</td>
<td>17.3±1.5 (5)</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>69.7±13.4 (5)</td>
<td>91.2±15.1 (5)</td>
<td>97.8±20.4 (4)</td>
</tr>
<tr>
<td>Ghrelin, pg/mL</td>
<td>123.5±23.5 (6)</td>
<td>87.7±15.3 (4)</td>
<td>101.4±22.5 (5)</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>7.20±1.33 (6)</td>
<td>16.79±3.48* (5)</td>
<td>10.96±2.46 (5)</td>
</tr>
<tr>
<td>HOMA index</td>
<td>1.2±0.2 (5)</td>
<td>2.4±0.6 (5)</td>
<td>2.7±0.6 (4)</td>
</tr>
</tbody>
</table>

Data expressed as mean±SE. HOMA index is insulin (μM)×glucose
(mmol/L)/22.5. Numbers in parentheses indicate sample size.

*P<0.05, OP>control.
TABLE 3. Organ Dimensions of Control, OP, and OR Rats

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obesity-Prone</th>
<th>Obesity-Resistant</th>
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</thead>
<tbody>
<tr>
<td>Heart, g</td>
<td>1.71±0.10</td>
<td>1.82±0.07</td>
<td>1.58±0.05</td>
</tr>
<tr>
<td>Heart weight/body</td>
<td>0.28±0.02</td>
<td>0.25±0.02</td>
<td>0.26±0.01</td>
</tr>
<tr>
<td>weight, g/100 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right + left kidneys, g</td>
<td>3.50±0.19</td>
<td>3.98±0.14†</td>
<td>3.39±0.13</td>
</tr>
<tr>
<td>Kidney weight/body</td>
<td>0.57±0.03</td>
<td>0.55±0.03</td>
<td>0.56±0.03</td>
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<tr>
<td>weight, g/100 g</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Liver, g</td>
<td>17.52±0.90</td>
<td>22.22±1.29*</td>
<td>17.14±0.87</td>
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<tr>
<td>Liver weight/body</td>
<td>2.84±0.13</td>
<td>3.07±0.12</td>
<td>2.83±0.12</td>
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<tr>
<td>weight, g/100 g</td>
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<tr>
<td>Gastrocnemius+</td>
<td>3.08±0.14</td>
<td>3.27±0.14</td>
<td>3.01±0.09</td>
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<td>soleus, g</td>
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</table>

Data expressed as mean±SE.
*P<0.05, OP>other groups; †P<0.10, OP>other groups.

fat weight in the present study was similar to fat weight in OP and control rats in a previous study (51 and 36 g, respectively) and higher than those in a later study (43 and 23 g, respectively). Importantly, these data demonstrate that the diet protocol yielded the desired body weight and body composition changes.

Despite increased body weight and fat, cardiac function was not significantly altered by the magnitude/duration of obesity used in this study. Cardiac structure/composition was not significantly altered by the magnitude/duration of obesity used in this study. Cardiac structure/composition was evaluated using echocardiography and histology. No group differences were found in chamber volume or collagen content. Whereas there were differences in wall thickness between OP and OR, wall thickness did not differ between

TABLE 4. Echocardiography Data From Control, OP, and OR Rats

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<tr>
<td>Diastolic measurements</td>
<td></td>
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<tr>
<td>LV posterior wall, mm</td>
<td>2.12±0.11</td>
<td>2.24±0.20†</td>
<td>1.77±0.08</td>
</tr>
<tr>
<td>LV diameter, mm</td>
<td>7.23±0.33</td>
<td>7.61±0.27</td>
<td>6.78±0.20</td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td>2.12±0.10</td>
<td>2.09±0.07</td>
<td>1.99±0.09</td>
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<td>Systolic measurements</td>
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<td>LV posterior wall, mm</td>
<td>3.50±0.13</td>
<td>4.00±0.28*</td>
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<tr>
<td>LV diameter, mm</td>
<td>3.20±0.44</td>
<td>3.07±0.53</td>
<td>2.65±0.24</td>
</tr>
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<td>Septal thickness, mm</td>
<td>3.52±0.13</td>
<td>3.93±0.25</td>
<td>3.68±0.21</td>
</tr>
<tr>
<td>Ejection time, ms</td>
<td>98.3±7.1</td>
<td>97.1±15.1</td>
<td>90.7±6.9</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>280.7±5.4</td>
<td>283.0±6.9</td>
<td>284.4±5.9</td>
</tr>
<tr>
<td>LVd/PW</td>
<td>3.45±0.23</td>
<td>3.54±0.42</td>
<td>3.84±0.15</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>56.4±3.8</td>
<td>60.2±5.8</td>
<td>60.9±3.2</td>
</tr>
<tr>
<td>Wall stress (diastole), kdynes/cm²</td>
<td>−0.03±1.12</td>
<td>−1.50±0.83</td>
<td>0.20±1.33</td>
</tr>
<tr>
<td>Wall stress (systole), kdynes/cm²</td>
<td>19.21±5.98</td>
<td>15.92±6.51</td>
<td>15.40±2.25</td>
</tr>
<tr>
<td>VCFr</td>
<td>280.3±36.3</td>
<td>321.5±62.8</td>
<td>318.7±36.3</td>
</tr>
<tr>
<td>Wall stress (systole)/LVESD</td>
<td>5.39±0.76</td>
<td>4.53±1.01</td>
<td>5.71±0.42</td>
</tr>
</tbody>
</table>

Data expressed as mean±SE. LVESD indicates left ventricular end diastolic diameter; PW, posterior wall; VCFr, velocity of circumferential shortening (rate corrected); LVESD, left ventricular end systolic diameter.
*P<0.05, OP>OR; †P<0.10, OP>OR.

OP and controls. It is not clear why this pattern emerged. Random differences in wall thickness at the start of the study, and/or differences in blood volume or endocrine activation (eg, renin–angiotensin system) may have occurred. However, other data argue against renin–angiotensin system activation in OR rats.

Function was evaluated using echocardiography and direct measurement of LV pressures, and no group differences were detected in FS, wall stress, velocity of circumferential shortening, LV pressure, or contractility/relaxation indices. We believe that this is the first study to document cardiac function in this model of diet-induced obesity. Our data suggest that although an 8- to 12-week diet protocol is sufficient to induce renal and arterial oxidative stress, it is not sufficient to produce changes in cardiac hypertrophy or global cardiac function.

Several factors have been implicated in the genesis of ventricular hypertrophy, including hypertension, volume load, age, salt intake, angiotensin II, and insulin. In the present study, insulin concentrations did not differ among groups. Telemetry recordings demonstrated that there was not a sustained increase in BP in OP, thus eliminating a major factor in producing hypertrophy. The lack of hypertrophy may have contributed to normal LV function in OP.

HR demonstrated a developmental effect, where week-12 values were significantly lower than control values. This pattern has also been seen in lean and obese rabbits on a 12-week diet protocol. In the present study, the decline in HR during the 12-week protocol was 30% greater in lean compared with obese rats, suggesting a modest obesity-related tachycardia. Higher heart rates have also been found in this rat model after 16 weeks of a moderate fat diet. However, our conclusion must be tempered since there were no significant group differences in either control or week-12 HR values.

The response of plasma cholesterol and triglycerides in this model is quite variable. The present data are in general agreement with data from earlier studies indicating that OP had increased plasma cholesterol. The present data also demonstrated that OP had increased hepatic cholesterol content. In some studies, increased cholesterol was related more to the MFD than to increased body weight. In contrast, other studies and our data indicated that both plasma and hepatic cholesterol were related more to body weight since
OR rats had cholesterol concentrations similar to controls. However, at least one study\textsuperscript{33} found no difference in either plasma cholesterol or triglycerides between controls and rats fed the MFD.

Interestingly, the homeostasis model assessment index was higher in fat-fed rats, independent of weight gain. This is in accord with data demonstrating that high-fat feeding per se\textsuperscript{34,35} induces insulin resistance. High-fat feeding may inhibit skeletal muscle cellular fatty acid oxidation via reduced AMP protein kinase activity and reduced Glut4 mRNA and protein content.\textsuperscript{34} Saturated fats in particular may impair muscle insulin sensitivity because of storage of lipid metabolites other than triglycerides.\textsuperscript{35} Other studies using the OP/OR model have not commented on this occurrence.

Limitations
Cardiac structure/function was measured under gas anesthesia; it is impossible to determine whether anesthesia differentially affected measurements among groups. However, structural measures such as wall thickness and cardiac collagen should not be affected by anesthesia. Further, HR under anesthesia did not differ among groups, minimizing the possibility that differences in filling time would affect diastolic volumes. Thus, available evidence suggests that anesthesia did not produce systematic differences.

Perspectives
Twelve weeks of a MFD in the OP/OR rat induced expected body weight/fat gains and lipid and endocrine abnormalities typical of obesity. However, average daily BP and HR, as well as diurnal rhythms of BP and HR, were not altered in OP rats. Further, echocardiographic and histological measures of cardiac structure and function did not differ among groups. Whereas the OP/OR rat model has been used successfully to study renal function in obesity, these data suggest that 12 weeks of a MFD is insufficient to produce global cardiac changes, particularly in the absence of hypertension. It is unknown whether a longer period of obesity and/or greater body weight/fat gains are necessary to induce cardiac changes in this model. Alternatively, this model may be useful in studying resistance to hypertension in obesity. These data highlight the possibility that obesity-related abnormalities in different organ systems may develop after varying periods of exposure to either a MFD or increased body weight in the OP/OR rat.

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None.

References


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