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 obese rat have been used for cardiovascular research.\(^4,5\) However, these models may not exhibit the same abnormalities as do obese humans, such as hypertension, hyperglycemia, hyperinsulinemia, and cardiac hypertrophy.\(^4,6\) In contrast, diet-induced models of obesity in the dog and rabbit have shown promise for studying cardiovascular\(^7-9\) and renal\(^10\) mechanisms involved in obesity-related pathologies.

There is little doubt that a rodent model of obesity based on the intake of a high-fat diet would be advantageous in studying obesity-related cardiovascular abnormalities. One such 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. Over time, rats diverge into an OP group that rapidly gains weight in comparison to normal chow-fed rats and an obesity-resistant (OR) group that gains weight at or below the rate seen in chow-fed rats. 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 models\(^9,16,17\) (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 16% kcal protein. The MFD consisted of 32% kcal fat, 51% kcal carbohydrate, and 17% kcal protein (Research Diets, New Brunswick, 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.18 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. For diurnal rhythms, group HR and BP values were compared during the control period and week 12 using repeated measures ANOVA.

**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>
<th>Obesity-Resistant</th>
</tr>
</thead>
<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>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control week</td>
<td>101.1±3.4</td>
<td>101.7±1.2</td>
<td>102.9±1.8</td>
</tr>
<tr>
<td>Week 12</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</td>
<td>10.5±1.9</td>
<td>12.1±1.9</td>
<td>6.2±3.0</td>
</tr>
<tr>
<td>Control week BP, beats/min</td>
<td>418.3±4.2</td>
<td>411.5±6.5</td>
<td>423.1±9.1</td>
</tr>
<tr>
<td>Week 12</td>
<td>370.6±4.9</td>
<td>379.7±4.2</td>
<td>385.5±7.4</td>
</tr>
<tr>
<td>Week 12-control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control week HR, beats/min</td>
<td>−47.7±2.6</td>
<td>−31.7±5.7*</td>
<td>−34.6±4.0</td>
</tr>
<tr>
<td>Week 12</td>
<td>48.3±8.6</td>
<td>58.3±4.3</td>
<td>58.1±6.8</td>
</tr>
<tr>
<td>Week 12-control</td>
<td>60.2±5.7</td>
<td>60.8±7.1</td>
<td>61.6±8.9</td>
</tr>
<tr>
<td>Control week BP, mm Hg</td>
<td>7.2±1.8</td>
<td>7.4±0.8</td>
<td>7.4±1.3</td>
</tr>
<tr>
<td>Week 12</td>
<td>5.4±1.1</td>
<td>4.9±2.0</td>
<td>5.0±0.7</td>
</tr>
</tbody>
</table>

Data expressed as mean±SE. *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

![Figure 1](http://hyper.ahajournals.org/)

Figure 1. Final body weight (upper left), weight gain (upper right), adipose tissue weight (lower left), and adipose weight/body weight ratio (lower right) in control, OP, and OR rats. *$P=0.05$, OP>other groups; **$P=0.05$, OP>controls.

![Figure 2](http://hyper.ahajournals.org/)

Figure 2. Body weight/blood pressure relationship over 12 weeks in control, OP, and OR rats. Slopes not significantly different: control=0.036 (solid line); OP=0.41 (dashed line); OR=0.036 (dotted line).
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), suggesting greater insulin resistance. 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, 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 ± 174, 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 humans7,9,23–25 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,11,12,15,26 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 studies,12,15,26,27 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.11,12,15 However, the tail cuff method may be susceptible to errors because of handling stress,28 but this is by no means universal.29 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.14 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,13 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 14), 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 study11 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 OP13 were also similar to present values. Total

### TABLE 2. Plasma Hormones and Glucose in Control, OP, and OR Rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obesity-Prone</th>
<th>Obesity-Resistant</th>
</tr>
</thead>
<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>
</tr>
</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 weight, g/100 g</td>
<td>0.28± 0.02</td>
<td>0.25± 0.02</td>
<td>0.26± 0.01</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 weight, g/100 g</td>
<td>0.57± 0.03</td>
<td>0.55± 0.03</td>
<td>0.56± 0.03</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>
</tr>
<tr>
<td>Liver weight/body weight, g/100 g</td>
<td>2.84± 0.13</td>
<td>3.07± 0.12</td>
<td>2.83± 0.12</td>
</tr>
<tr>
<td>Gastrocnemius+ soleus, g</td>
<td>3.08± 0.14</td>
<td>3.27± 0.14</td>
<td>3.01± 0.09</td>
</tr>
</tbody>
</table>

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

Despite increased body weight and fat, cardiac function was not significantly altered by the magnitude/duration of the diet protocol yielded the desired body weight and body composition changes. The response of plasma cholesterol and triglycerides in this model of diet-induced obesity may have contributed to normal LV function in OP.32

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 data13 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,12,15 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.30–32 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.32

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.25 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.12

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 studies1,13 indicating that OP had increased plasma cholesterol. The present data also demonstrated that OP had increased hepatic cholesterol content. In some studies,13 increased cholesterol was related more to the MFD than to increased body weight. In contrast, other studies13 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 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 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. Saturated fats in particular may impair muscle insulin sensitivity because of storage of lipid metabolites other than triglycerides. 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.

**Acknowledgments**

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