Refeeding Hypertension in Obese Spontaneously Hypertensive Rats

Paul Ernsberger, Richard J. Koletsky, Jon S. Baskin, Mary Foley

Abstract Very-low-calorie diets lower blood pressure acutely in obese humans and rats. However, refeeding after dietary restriction produces mild hypertension in rats. Refeeding hypertension was characterized in genetically obese spontaneously hypertensive rats (obese SHR, Koletsky rat), a model of genetic obesity and hypertension. Obese SHR were fed a restricted diet (Optifast) for 12 days, refed ad libitum for 28 days, and then refed 4 days and killed. Control obese SHR and lean SHR littermates were fed ad libitum continuously. Dietary restriction led to rapid weight loss followed by prompt regain to baseline weight after return to unrestricted food intake. Heart rate fell with institution of the low-calorie diet and returned to baseline on refeeding. Blood pressure became elevated during refeeding in dieted obese SHR relative to ad libitum fed obese SHR controls. The fall in blood pressure after ganglionic blockade with chlorisondamine was exaggerated in refed obese SHR, and cardiac β-adrenergic receptors were downregulated. Both of these findings imply increased sympathetic tone. The left ventricular wall was thicker in the refed obese SHR than in the ad libitum fed obese SHR. Shorter cycles of weight loss and regain in lean SHR led to transient increases in blood pressure and heart rate. Cycles of dietary restriction and refeeding in obese SHR elicited sustained blood pressure elevation via sympathetic activation and exacerbate cardiac hypertrophy. Drastic fluctuations in nutrient intake may not be advantageous in hypertension.

Key Words • receptors, adrenergic, beta • rats, inbred SHR • fasting • diet • weight gain • weight cycling

Obesity and hypertension commonly accompany each other in human populations, but the mechanism associating these two conditions remains unknown, primarily because of limitations in animal models for obesity-related hypertension. Hyper- tension and obesity coexist in the obese spontaneously hypertensive rat (SHR) (Koletsky) strain. These rats carry a genetic predisposition to hypertension upon which a syndrome of genetic obesity is superimposed. The obese phenotype is thought to be caused by a single recessive gene (fa) related to the Zucker fatty trait (fa). When two heterozygous (Fa/fa) phenotypically lean rats mate, about one fourth of their offspring will be obese (fa/fa). Obese SHR are sterile, so the Koletsky strain was maintained through more than 50 generations of brother-sister mating of lean heterozygotes.

Obese humans frequently alternate between dietary restriction and bingeing and show repeated cycles of weight loss and regain. These body weight fluctuations have been shown to have deleterious cardiovascular effects and increase mortality. The mechanism for the untoward cardiovascular effects is unknown. We sought to reproduce the typical "yo-yo syndrome" or weight cycling pattern in an obese hypertensive animal model. In most studies, obese animals maintain steady body weights and consume a constant amount of food on a day-to-day basis, in contrast to obese humans. We previously reported that animals made obese by overfeeding remained normotensive if allowed to gain weight continuously but developed hypertension when subjected to cycles of weight loss and regain. Blood pressure fell during 4 days of dietary restriction, but during regain of weight after ad libitum feeding was reintroduced, blood pressure rose, overshot the original level, and attained mildly hypertensive levels. Because hypertension occurs during the refeeding period after dietary restriction, it is known as refeeding hypertension. The mechanism for the blood pressure rise during refeeding was proposed to be an increase in sympathetic activity, because the heart rate response to β-adrenergic blockade was increased and cardiac β-adrenergic receptors were downregulated. The latter finding is consistent with chronic overstimulation of β-receptors by excess catecholamines in the heart. A link between patterns of caloric intake and sympathetic activity has been previously established.

In the present study, we examined refeeding hypertension in genetically obese animals maintained on a diet of a normal composition, rather than high sucrose or high fat diets, which might themselves affect blood pressure. Obese SHR are not only genetically obese but also inherit a propensity toward hypertension, making these animals ideal subjects for the study of the cardiovascular effects of refeeding. We sought to determine the effect of cycles of weight loss and regain on hypertension in obese SHR compared with control obese and lean rats fed continuously ad libitum. A separate group of lean SHR was subjected to 4 days of dietary restriction followed by refeeding for the purpose of comparison with previous studies in overfed Sprague-Dawley rats. For obese SHR, we used a 12-day period of dietary restriction to maximize the magnitude of weight fluctuations.
Methods

Animals

Obese SHR (n=21) and their lean littermates (n=16) were housed in a separate limited-access room of the animal facility and kept in individual cages throughout the study. Obese SHR have been maintained as a closed colony since 1970 and propagated by continuous brother-sister mating for more than 20 years. They were provided with standard chow (Ralston-Purina) and water ad libitum unless stated otherwise. Both male (n=10) and female (n=27) animals were used. Initial ages at the start of baseline measurements were 5 to 24 weeks. The four experimental groups (obese control, obese dieted-refed, lean control, and lean dieted-refed) were matched for age and sex. In most cases, the matched animals assigned to the four groups were littermates. At the termination of the experiment, the control rats were 221 ± 13 days of age and the dieted-refed rats were 217 ± 14 days of age.

Blood Pressure and Heart Rate Measurements in Conscious Animals

Systolic blood pressure and heart rate were measured by tail-cuff electrophygmononometer as previously described. Before any measurements were recorded, the rats were familiarized with the apparatus. After 5 minutes in a warming chamber at approximately 38°C, rats entered a darkened Plexiglas restrainer, and the tail was warmed by a heating strip maintained at 40°C until a pulse was detected over the tail artery (usually within 3 minutes). Four measurements of systolic blood pressure were taken at 1-minute intervals using a constant rate of inflation and deflation of the tail cuff (15 mm Hg/second). The rats were then immediately allowed to climb out of the restrainer into the home cage. Vocalizations and struggling were only occasionally observed in lean SHR and never in the obese animals. Heart rate was determined from the pressure wave recording. During an initial baseline period, obese and lean SHR were weighed three times a week, and blood pressure and heart rate were measured twice weekly until stable readings were obtained, indicating habituation to the blood pressure measuring procedure. The mean of the last three blood pressure and heart rate readings was taken as the baseline.

Very-Low-Calorie Diet

Chow was taken away from rats of the dieted-refed group, and they were instead given Optifast 800 (chocolate flavor). Optifast was given in an amount equal to one sixth of the baseline caloric intake and provided to each rat daily an average of 14 kcal, 1.3 g protein, 45 mg potassium, 22 mg sodium, 19 mg calcium, and 7.6 mg magnesium, plus trace minerals and vitamins. Optifast was given in the late afternoon every day for 12 days in obese SHR and 4 days in lean SHR and was consumed promptly. Optifast was given as either a powdered food or a suspension in water with equivalent results. Sodium intake averaged 66 mg/d at baseline and 22 mg/d during Optifast feeding. Free access to chow was restored at the end of the dietary restriction period, and ad libitum feeding was continued for 28 days in obese SHR and 40 days in lean SHR. Rats had free access to tap water at all times. Blood pressure, heart rate, and body weight were determined at frequent intervals during the dietary restriction and refeeding periods.

To test for effects specific to the composition of Optifast itself, in a separate group of eight obese SHR, half were maintained as ad libitum controls, and half the animals were fed one sixth of the baseline caloric intake as standard rat chow instead of Optifast. These animals were then subjected to the same weight cycling protocol as described above.

Terminal Measurements

The experiment was terminated after 4 days of refeeding following the second fast because previous studies had indicated that this was the point at which the blood pressure elevation caused by refeeding was first fully developed. Rats were anesthetized with urethane (1 g/kg IP), and the femoral or brachial artery was cannulated for direct measurement of arterial blood pressure. After a stable baseline was obtained, each rat was injected with chlorisondamine (0.4 mg IP), and arterial pressure readings were repeated 15 minutes later when readings had stabilized at a lower level. The kidney and heart were removed, blotted to remove blood, and weighed. Left ventricular wall thickness was measured with calipers, and the ventricle was flash frozen for later assay of β-adrenergic receptor binding. To examine the possible influence of age on ventricular wall thickness, we determined the correlation between age and heart wall thickness in control obese rats and found it to be -0.400, which is not significant (P=0.18).

Cardiac β-Adrenergic Receptor Binding Assays

Cardiac ventricles were slowly thawed, minced, and homogenized in 20 vol ice-cold HEPES-buffered isotonic sucrose (pH brought to 7.4 with Tris base) containing the protease inhibitors 1,10-phenanthroline (0.1 mmol/L) and phenylmethylsulfonyl fluoride (50 mmol/L) by using a polytron (Tekmar Tissue-Mizer, setting 80 for 2x15 seconds). Homogenates were centrifuged at 10000g for 5 minutes at 4°C to remove nuclei and debris. The pellets (P1) were resuspended in 20 mL of homogenization buffer and centrifuged again at 10000g for 5 minutes. The combined supernatants were centrifuged at 48 000g for 18 minutes at 4°C, and the resulting P2 pellet was resuspended in 10 to 25 vol of 50 mmol/L Tris-HCl buffer (pH 7.7) containing 5 mmol/L EDTA. After recentrifugation at 48 000g for 18 minutes, the resulting membrane pellet was resuspended in Tris-HCl containing 25 mmol/L NaCl, preincubated for 30 minutes at 25°C, chilled on ice, centrifuged again, resuspended a final time in Tris-HCl alone, centrifuged, flash frozen, and stored at −70°C for up to 3 months.

Radioligand binding assays with [3H]-pindolol for determination of specific binding to β-adrenergic receptor sites were performed by a modification of methods previously described. Membranes were slowly thawed and resuspended in Tris-HCl buffer (50 mmol/L, pH 7.7 at 25°C) at a concentration of 1 mg protein/mL. Assays were conducted in a total volume of 250 mL in polypropylene 96-well plates (Beckman Macrowell); each well contained 125 mL membrane suspension, 25 mL radioligand, and 100 mL (–)-isoproterenol or 0.1% ascorbic acid vehicle. Incubations were initiated by the addition of membrane and were carried out for 60 minutes at 25°C. Nonspecific binding was defined in the presence of (–)-isoproterenol (0.1 mmol/L). Cardiac membranes were incubated in triplicate with eight concentrations of [3H]-pindolol ranging from 1.0 to 100 pmol/L in the presence and absence of 0.1 mmol/L (–)-isoproterenol. Incubations were terminated by vacuum filtration over Reeves-Angel glass fiber filters using a cell harvester (Brandel). The filters were washed four times with 5 mL ice-cold Tris-HCl and read in a gamma counter. Protein was assayed by the method of Peterson.

Materials

[3H]-Pindolol (2200 Ci/mmol) was obtained from New England Nuclear, stored at −20°C in ethanol, and diluted in water before assay. Other compounds were obtained from Sigma Chemical Co.

Statistical Analysis

All values are given as mean±SEM. Repeated measures ANOVA was used for multiple time point data and one-way ANOVA for terminal measurements. Control and dieted-refed groups were compared for each phenotype, but comparisons of the effect of weight cycling in obese and lean rats were not made because of differences in the length of dietary restriction tolerated by the different phenotypes. Untreated control obese and lean littermates were compared to determine phenotype effects. Group means were compared by using the Newman-
Results

Body Weight

Obese SHR lost 91±5 g during 12 days of dietary restriction (Fig 1, bottom) but regained significantly more weight during the subsequent refeeding period (150±7 g; P<.01, Newman-Keuls). At the end of the first refeeding period, the dieted-refed obese SHR were within 5% of the weight of control obese SHR. During the second period of dietary restriction, the obese SHR lost less weight than during the first diet, either as an absolute amount (80±4 versus 91±5 g; P<.05, Newman-Keuls) or as a percentage of starting weight (15.7±0.4% versus 19.1±0.6%; P<.05, paired t test). The dieted-refed obese SHR remained significantly leaner than controls fed ad libitum at the end of the experiment, because the 4-day refeeding period after the end of the second dietary restriction was not sufficient for complete regain of lost weight. The control obese SHR gradually regained approximately 10% above their initial body weight over the course of the experiment.

Blood Pressure in the Conscious State

Repeated measures ANOVA indicated a significant effect of the dietary restriction and refeeding regimen on systolic blood pressure measured by the tail-cuff method in obese SHR [F(15,216)=4.8, P<.01]. Control obese SHR showed no change in blood pressure over the same period. Obese SHR failed to show a fall in blood pressure during the first 12-day trial of dietary restriction (Fig 1, top), despite rapid weight loss. In fact, blood pressure rose slightly (9±3 mm Hg) above baseline by the 12th day of dietary restriction (P<.05, Newman-Keuls). In another group of animals fed standard rat chow to the same degree of caloric restriction as the Optifast diet, after 12 days blood pressure rose from 171±3 to 181±5 mm Hg, whereas in the ad libitum fed control groups blood pressure did not change (172±4 versus 174±7 mm Hg). This indicates that the small increase in pressure during dietary restriction is not specific to Optifast.

Blood pressure rose abruptly with the reintroduction of regular chow feeding to a level approximately 20 mm Hg above baseline (P<.05, Newman-Keuls) and remained elevated throughout the 28-day refeeding period. Comparable results were obtained after restricted feeding of standard chow (data not shown). In contrast to the first fast, blood pressure fell during the second dietary restriction (11.3±4.6 mm Hg on the 4th day; P<.05, Newman-Keuls). Blood pressure returned to its previous elevated level during the final refeeding period.

Heart Rate

Repeated measures ANOVA indicated a significant effect of the dietary restriction and refeeding regimen on heart rate in obese SHR [F(14,207)=9.3, P<.01]. Control obese SHR showed no change in heart rate over the same period. During both episodes of dietary restriction, obese SHR developed bradycardia by the 4th day and remained bradycardic until the 12th day (Fig 1, middle). Heart rate promptly returned to baseline upon refeeding. Relative tachycardia was observed at only a single time point after extended refeeding. Unlike blood pressure, heart rate showed no tendency to overshoot after dietary restriction.

Direct Arterial Blood Pressure

Direct measurement of arterial blood pressure with rats under urethane anesthesia showed that refeeding hypertension persisted in the obese SHR, with diastolic, mean, and systolic pressures all significantly elevated over control values (Fig 2). Direct arterial pressures were lower in control obese SHR than in control lean SHR (P<.05 for systolic, mean, and diastolic blood pressures by ANOVA), confirming tail-cuff measurements.

Chlorisondamine was administered to each rat to eliminate the contribution of the sympathetic nervous system to blood pressure maintenance. Refeeding hypr-
TABLE 2. Cardiac β-Adrenergic Receptor Binding in Obese and Lean SHR: Effect of Refeeding

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>(B_{\text{max}}, \text{fmol/mg Protein})</th>
<th>(K_d, \text{pmol/L})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese SHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=3)</td>
<td>23±4</td>
<td>82±16</td>
</tr>
<tr>
<td>Dieted-refed (n=3)</td>
<td>13±1*</td>
<td>45±4*</td>
</tr>
<tr>
<td>Lean SHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=4)</td>
<td>26±2</td>
<td>62±7</td>
</tr>
<tr>
<td>Dieted-refed (n=3)</td>
<td>21±2</td>
<td>45±5</td>
</tr>
</tbody>
</table>

SHR indicates spontaneously hypertensive rats. \(B_{\text{max}}\) is defined as estimated maximal density of receptor binding sites; \(K_d\) is the dissociation constant and is inversely proportional to the radioligand affinity. Values are mean±SEE from nonlinear curve-fitting analysis of eight-point saturation curves using \(^{125}\text{I}\)-pindolol to label β-adrenergic receptors. Nonspecific binding in presence of 0.1 mmol/L (−)-isoproterenol was subtracted from total binding. Data from three to four rats tested within each group were analyzed simultaneously.

*Significant effect of dietary restriction and refeeding regimen, \(P<.05\).

from their higher body weights. After correction for body weight, relative organ weights were significantly decreased in obese relative to lean SHR. Neither absolute nor relative organ weights were affected by dietary restriction and refeeding. The ventricular wall was thicker in control obese SHR heart than in the lean controls. Cycles of dietary restriction and refeeding led to a nearly 10% further thickening of the ventricular wall in obese SHR.

Cardiac β-Adrenergic Receptor Binding

Refeeding hypertension in obese SHR was associated with a loss of more than 40% of the β-adrenergic receptors in the cardiac ventricle (Table 2). Radioligand binding affinity was increased. Obese and lean controls did not differ from each other.

Effects of Short Cycles of Refeeding on Lean SHR

For comparison with previous studies in dietary obese rats using 4 days of dietary restriction, lean SHR were dieted 4 days and then refed. Lean SHR rapidly lost weight during 4 days of dietary restriction and regained weight equally rapidly during the first 4 days of refeeding (Fig 3). The body weight of dieted-refed lean SHR

Organ Weights and Heart Wall Thickness

The kidneys and heart of obese SHR were heavier than those of lean SHR (Table 1), as would be expected

Table 1. Heart and Kidney Weights and Ventricular Wall Thickness in Obese and Lean SHR: Effect of Refeeding

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Kidney Weight</th>
<th>Heart Weight</th>
<th>Ventricular Wall Thickness, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g</td>
<td>g/kg</td>
<td>g</td>
</tr>
<tr>
<td>Obese SHR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=10)</td>
<td>2.9±0.1†</td>
<td>5.1±0.3†</td>
<td>1.49±0.04†</td>
</tr>
<tr>
<td>Dieted-refed (n=11)</td>
<td>2.7±0.2†</td>
<td>4.9±0.2†</td>
<td>1.38±0.08†</td>
</tr>
<tr>
<td>Lean SHR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=8)</td>
<td>2.1±0.2</td>
<td>7.1±0.1</td>
<td>1.10±0.06</td>
</tr>
<tr>
<td>Dieted-refed (n=8)</td>
<td>2.0±0.2</td>
<td>7.3±0.2</td>
<td>1.15±0.08</td>
</tr>
</tbody>
</table>

SHR indicates spontaneously hypertensive rats. Values are mean±SEM.

†Significant difference between obese and lean SHR, \(P<.05\) by ANOVA.

*Significant effect of dietary restriction and refeeding regimen, \(P<.05\) by ANOVA.
agreement with prior experiments in obese SHR of this colony that showed persistent increases in blood pressure after intake of normal rat chow was restricted 50%. Additionally, the failure to observe a fall in blood pressure during dietary restriction was not due to the use of Optifast, because the same degree of dietary restriction using normal rat chow also failed to lower blood pressure. It might be argued that behavioral effects of hunger might have maintained blood pressure levels during restrictive feeding. However, this appears unlikely because blood pressure did fall significantly in obese SHR during the second period of restricted feeding.

Lean SHR were subjected to shorter periods of dietary restriction for comparison with previous studies of 4-day fasting periods in Sprague-Dawley rats. The brief period of nutrient restriction of lean SHR is not comparable to the prolonged restriction of obese SHR, which were able to tolerate substantial weight loss. In lean SHR, lost body weight was regained as quickly as it was lost after return to unrestricted feeding. Blood pressures were significantly elevated above baseline during both refeeding periods but were not increased in the anesthetized state. These findings are comparable to those previously reported in overfed Sprague-Dawley rats, with the exception that hypertension persisted under anesthesia in Sprague-Dawley rats. In another study, blood pressure was increased in refed rats housed in groups but not those housed individually. In the present study, all rats were individually housed, suggesting that housing conditions do not play a major role in modulating refeeding hypertension.

The elevation of blood pressure by refeeding in obese SHR after 12 days of dietary restriction was greater than that seen after 4 days of similar dietary restriction in either lean SHR or Sprague-Dawley rats. In the previous study in overfed Sprague-Dawley rats, refeeding increased wall thickness by 7%, but this effect did not reach statistical significance. In obese SHR, refeeding increased wall thickness 9%, which reached significance. There was also a greater downregulation of cardiac β receptors in refed obese SHR (40% versus 29% in refed Sprague-Dawley rats). In previous studies of Sprague-Dawley rats, cycles of nutrient restriction and refeeding resulted in a threefold greater heart rate response to β-adrenergic blockade, consistent with increased sympathetic tone. In the present study, β-adrenergic agents were not given so as to avoid interfering with postmortem radioisland binding assays.

Rats fed a lard-sucrose diet for 1 year show a slight increase in blood pressure when measured in conscious animals by tail cuff, but direct arterial pressures with rats under anesthesia are unchanged. Dietary obesity has no effect on blood pressure in normal rats, and obesity-promoting diets actually attenuate hypertension in SHR. Dogs become hypertensive when their daily diet is supplemented with 1 kg lard, but it is not clear whether the pressor effect is due to increased saturated fat intake or adiposity itself. Rats made obese by hypothalamic lesions are normotensive and in fact are resistant to the induction of experimental hypertension, despite increased sodium intake caused by hyperphagia. Zucker fatty rats have been proposed as a model of human obese hypertension, but most studies have found Zucker rats to have pressures equal to lean littermates or elevated only slightly (approximately 10 mm Hg). Furthermore, restriction of food intake, although normalizing body weight, did not lower blood pressure in hypertensive Zucker rats. Feeding of a high salt diet failed to increase blood pressure in Zucker obese rats. Thus, obese animal models are not reliably accompanied by obesity-related hypertension.

The cardiovascular effects of refeeding after dietary restriction have not been examined in genetically obese animals, although metabolic changes have been evaluated. The cardiovascular effects of weight cycling have been characterized in dogs and pigs. Dogs develop refeeding hypertension during regain of weight after dietary restriction, and the elevation in blood pressure is attenuated by surgical sympathectomy. The present study confirms the role of sympathetic overactivity in refeeding hypertension. Weight cycling in pigs produced elevations in blood pressure, adverse electrocardiographic changes, focal myocardial fibrosis, and arteriolar thickening. The mechanisms for these pathological processes remain to be determined.

Increasing evidence has shown that repeated cycles of weight loss and regain are harmful to human health. Epidemiological evidence shows that men who show large fluctuations in weight from 20 to 40 years of age have increased systolic and diastolic blood pressures and cholesterol levels. These "yo-yo dieters" are two times more likely to die of coronary heart disease, even after adjustment for known risk factors, than are men with stable or steadily increasing weight. In fact, the risk of weight fluctuations accounted for nearly all the excess risk associated with obesity. Another study of adult men linked weight cycling to increases in cardiovascular and total mortality of up to twofold. In the National Health and Nutrition Examination Survey, obese subjects who lost weight during follow-up showed a twofold increase in mortality after adjustment for risk factors and previous illness. Epidemiological studies have not offered potential mechanisms for the deleterious effects of weight fluctuations, but laboratory investigations such as the present study implicate cardiovascular and metabolic processes. We show for the first time in the present study that cycles of weight loss and regain may be an important overlooked factor in the relation between obesity and hypertension.

The refeeding obese SHR is a potential model for human obese hypertension. Common features shared with essential hypertension in obese humans are increased sympathetic tone and the hyperinsulinemia and insulin resistance previously reported in obese SHR. The increase in ventricular wall thickness in refed obese SHR is also a hallmark of cardiac changes in human obese hypertension. In humans, as in the obese SHR, ventricular wall thickness increases during refeeding after dietary restriction. Obese SHR spontaneously develop kidney disease after 6 months of age, which models renal disease in human hypertension and diabetes mellitus. Obese hypertensive humans exhibit a depressor response to dietary restriction, although not all subjects show this effect. After a cycle of weight loss and regain, obese SHR showed a prompt depressor response to dietary restriction similar to that seen in obese hypertensive humans. The appearance of a depressor response to dietary restriction may be caused by-
creased sympathetic tone, consistent with models linking sympathetic activity to caloric intake.15

The present study characterizes an animal model for the adverse consequences of rapid weight loss and regain. The frequent loss and regain of large amounts of weight is the norm in the obese population.17 Many dietary restriction programs emphasize benefits of rapid weight loss in obese hypertension. No information had been available on the effects of rapid weight loss and regain superimposed on a background of obese hypertension. The results of this study suggest that greater emphasis should be placed on permanent lifestyle changes for obese hypertensive individuals rather than rapid weight loss with drastic dietary restriction.

Acknowledgments

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