Obesity-Induced Hypertension
Renal Function and Systemic Hemodynamics
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This study examined the control of renal hemodynamics and tubular function, as well as systemic hemodynamics, during obesity-induced hypertension in chronically instrumented conscious dogs. Mean arterial pressure, cardiac output, and heart rate were monitored 24 hours a day using computerized methods, water and electrolyte balances were measured daily, and renal hemodynamics were measured each week during the control period and 5 weeks of a high-fat diet. After 7 to 10 days of control measurements, 0.5 to 0.9 kg of cooked beef fat was added to the regular diet, and sodium intake was maintained constant at 76 mmol/d throughout the study. After 5 weeks of the high-fat diet, body weight increased from 24.0±1.0 to 35.9±4.9 kg, mean arterial pressure increased from 83±5 to 100±4 mm Hg, cardiac output increased from 2.86±0.27 to 4.45±0.55 L/min, and heart rate rose from 68±5 to 107±9 beats per minute. Associated with the hypertension was an increase in cumulative sodium balance to 507±107 mmol after 35 days and a rise in sodium iothalamate space, an index of extracellular fluid volume, to 131±4% of control. Sodium retention was due to increased tubular reabsorption, because glomerular filtration rate and effective renal plasma flow increased throughout the 5 weeks of the high-fat diet, averaging 135±4% and 149±19% of control, respectively, during the fifth week of the high-fat diet. Plasma renin activity and plasma insulin concentration increased from 0.46±0.12 ng angiotensin I/mL per hour and 11.1±2.6 μU/mL, respectively, to 1.10±0.23 ng angiotensin I/mL per hour and 30.1±7.0 μU/mL after 5 weeks. Because decreased sodium excretion occurred despite elevated mean arterial pressure, obesity-induced hypertension in dogs is associated with a shift of renal pressure natriuresis that is caused by increased tubular reabsorption, although the exact mechanism by which this occurs is still unclear. (Hypertension. 1993;22:292-299.)

KEY WORDS • obesity • sodium • kidney • glomerular filtration rate • insulin • cardiac output • renin

Weight gain appears to be an important factor in elevating blood pressure in many essential hypertensive individuals.1-4 Epidemiological studies have shown that hypertension is more prevalent in obese than in nonobese individuals and that blood pressure is correlated to body weight, even in normotensive subjects.1-5 Experimental studies have demonstrated that weight gain, even over a period of a few weeks, consistently elevates blood pressure and weight loss decreases blood pressure independent of changes in sodium intake.6-10 Although this association between obesity and hypertension is widely recognized, the mechanisms responsible for weight-related changes in blood pressure have not been elucidated.

Much of the evidence for various mechanisms postulated to cause obesity-induced hypertension derives from studies that have attempted to correlate various abnormalities in obesity with hypertension. Establishing cause-and-effect relations has been hampered by the lack of suitable animal models that mimic obesity-induced hypertension in humans and that allow sequential changes in renal, endocrine, and cardiovascular function to be monitored during the development of obesity. In 1939, Wood and Cash6 developed an experimental model of obesity-associated hypertension by feeding dogs a high-fat diet. However, the mechanisms responsible for hypertension were not determined, and there has been very little effort in the past 50 years to further develop large-animal models of obesity. Rocchini and colleagues7-8 have demonstrated that dogs fed a high-fat diet have many of the characteristics of obese humans, including hyperinsulinemia, insulin resistance, sodium retention, and hypertension. However, the physiological mechanisms that lead to sodium retention and hypertension during the development of obesity are still unclear.

The present study was designed to determine the renal mechanisms responsible for sodium retention in obesity by examining the sequential changes in renal hemodynamics, tubular reabsorption, and electrolyte excretion that occur during weight gain in dogs fed a high-fat diet. In addition, we characterized changes in systemic hemodynamics during normal daily activities, as well as during periods of rest, during the development of obesity by monitoring arterial pressure, cardiac output, total peripheral resistance, stroke volume, and heart rate on a beat-by-beat basis, 24 h/d using computerized methods. Because of the recognized importance of various hormone systems, such as the renin-angioten-
sin system, in influencing renal function and blood pressure regulation, we also studied the endocrine changes associated with obesity.

Methods

Experiments were conducted in chronically instrumented mongrel dogs that were conditioned before study. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center and were carried out according to the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and according to the guidelines of the Animal Welfare Act.

Surgical procedures were performed with dogs under pentobarbital sodium anesthesia (30 mg/kg) and using aseptic conditions. Tygon (Norton Plastics, Akron, Ohio) catheters were implanted in the femoral arteries and veins for measurement of arterial pressure and blood sampling. All catheters were tunneled subcutaneously, exteriorized in the scapular region for protection, and fitted with a heparin solution (1000 USP units/mL). An electromagnetic flow probe (Zepeda Instruments, Seattle, Wash) was implanted around the ascending aorta through an incision at the fourth intercostal space, and the leads were exteriorized in the scapular region. After surgery, the dogs were permitted to recover, antibiotics were administered daily, and rectal temperatures were monitored to ensure that the dogs were afebrile throughout the studies.

After a recovery period of 1 to 2 weeks, the dogs were placed in individual metabolic cages in a quiet air-conditioned room with a 12-hour light/dark cycle and fitted with harnesses containing a pressure transducer (Statham Medical Instruments, Hato Rey, Puerto Rico) at the level of the heart. Arterial pressure signals were recorded on a polygraph (model 7D, Grass Instruments, Quincy, Mass) and sent to an analog-to-digital converter and analyzed with a digital computer (Turbo X-T, PC's Limited, Austin, Tex) using software developed in our laboratory. Analog signals from the polygraph were sampled in bursts of 12 seconds each minute, 24 hours a day, and the digitized data were processed on the computer to determine systolic, diastolic, and mean arterial pressures and heart rates. Cardiac output signals were monitored with an electromagnetic flowmeter (Zepeda Instruments) throughout the day. Analog signals from the flowmeter were sampled in bursts of 12 seconds each minute, 24 hours a day, along with the arterial pressure signals. Aortic flow signals were processed on the computer to determine stroke volume, cardiac output, peak aortic flow, and baseline diastolic flow. By comparing the diastolic flow baseline to the previously calibrated zero voltage baseline, baseline drift of the flow probe could be corrected on a beat-by-beat basis to allow precise determinations of cardiac output. Total peripheral vascular resistance was computed on a beat-by-beat basis using the cardiac output and arterial pressure signals. The average arterial pressure, heart rate, cardiac output, and total peripheral resistance for each day were calculated from values recorded over an 18-hour period between 2 PM and 8 AM. All routine care of the dogs, including feeding and cleaning of cages, and studies of renal function and blood sampling were done between 8 AM and 2 PM.

One of the venous catheters was connected to a roller infusion pump (model 375A, Sage Instruments, Cambridge, Mass) that delivered approximately 450 mL/d of sterile isotonic saline. The saline solution was pumped through a disposable filter (0.22 μm, Cathives; Millipore Corp, Bedford, Mass) to prevent air bubbles, contaminants, or bacteria from passing into the infusion catheter. The infusion tubing and cables from the pressure transducers and flow probes were protected by a flexible vacuum hose attached to the harness that permitted the dogs to move freely in the cages.

Throughout the study, dogs were fed two cans (447 g per can) per day of a sodium-deficient diet (H/D, Hill's Pet Products, Topeka, Kan) that provided approximately 7 mmol sodium and 65 mmol potassium per day and were given 5 mL of a vitamin syrup (VAL Syrup, Ft Dodge Labs, Ft Dodge, Iowa). Total sodium intake, including the food and the intravenous infusion of sodium chloride, was held constant throughout the study at approximately 76 mmol/d.

Experimental Protocol

After the dogs were placed in metabolic cages and the intravenous infusions were started, 10 to 14 days were allowed for the dogs to achieve sodium balance and for the acquisition of stable control measurements. During that time, dogs were trained to lie quietly while blood samples were obtained from the arterial catheters and studies of renal function were performed. After a week of stable control measurements, cooked beef fat (0.5 to 0.9 kg) was added to the regular diet of the dogs (n=7). The high-fat diet was continued for 5 weeks while systemic hemodynamics were monitored continuously and blood samples and renal function studies were conducted each week.

Although control measurements were made before the high-fat diet was started, we also studied an additional group of dogs (n=4) as a time control. In these experiments, the same protocol was followed as described above, except that the regular diet was maintained during the control and 5-week experimental periods. Measurements of systemic hemodynamics and renal function were made according to the schedule described above.

Analytic Methods

Glomerular filtration rate (GFR) and effective renal plasma flow were estimated from the total clearances of 125I-iothalamate (Glofil, Isotex Diagnostics, Friendswood, Tex) and 131I-iodohippurate (Hippuran, E.R. Squibb & Sons Inc, Princeton, NJ), respectively, as previously described.11 The distribution space of 125I-iothalamate was used as an index of extracellular fluid volume. Plasma and urine sodium and potassium concentrations were determined with ion-specific electrodes (Nova Biomedical, Waltham, Mass). Plasma and urine chloride concentrations were measured by coulometric titration with a chloridometer (Haake-Buchler, Saddlebrook, NJ). Plasma protein concentration was measured by refractometry (TS Meter, American Optical, Buffalo, NY), and plasma glucose concentration was determined by the hexokinase method (Sigma Diagnostics, St Louis, Mo).

Plasma renin activity was measured by radioimmunoassay using 125I-angiotensin I from New England Nu-
clear, Boston, Mass, and antibody from Chemicon, El Segundo, Calif. Aldosterone was extracted from plasma with 7 vol of dichloromethane, and the dried extract was reconstituted with phosphate gelatin buffer and measured by radioimmunoassay using 125-I-aldosterone from Amersham and liquid phase antibody (both from Diagnostic Products, Los Angeles, Calif). Plasma insulin concentration was measured by radioimmunoassay (Diagnostic Products). Plasma epinephrine and norepinephrine concentrations were measured by high-performance liquid chromatography with electrochemical detection. Before assay, the catecholamines were absorbed on alumina. Plasma atrial natriuretic peptide (ANF) concentration was measured by radioimmunoassay. ANF was extracted from 1 mL of plasma by reversed-phase liquid chromatography using a MilliLab 1A workstation and C18 cartridges (Sep-Pak Plus, Waters Chromatography Division, Milford, Mass). 125-I-labeled ANF tracer (New England Nuclear) was added to plasma pools for the estimation of recovery of unlabeled ANF from the sample. 125-I-ANF recovery averaged 85±10% of the added tracer. After evaporation, the extract was dissolved in cold assay buffer and aliquots were used for radioimmunoassay using antibody obtained from Research and Diagnostic Antibodies, Berkeley, Calif. Interassay and intra-assay coefficients of variation were 7.2% and 11.2%, respectively. Values were corrected for percent recovery.

Statistical Analyses

Experimental data were compared to control data using analysis of variance and Dunnett’s t test for multiple comparisons,13,14 Statistical significance was considered at a value of P<.05. All data are expressed as mean±SEM unless otherwise indicated.

Results

Feeding dogs a high-fat diet for 5 weeks caused parallel increases in body weight and mean arterial pressure (Fig 1). Body weight increased from a control value of 24.0±1.0 to 35.9±4.9 kg after 5 weeks of the high-fat diet. Mean arterial pressure did not change significantly during the first week of the high-fat diet but by the second week was significantly elevated and continued to increase during the first 4 weeks. During the fifth week of the high-fat diet, mean arterial pressure averaged 17±2 mm Hg above control. Systolic pressure increased from 128±6 to 149±8 mm Hg, and diastolic pressure increased from 66±4 to 80±3 mm Hg after 35 days of the high-fat diet.

Cardiac output increased by approximately 56% during the high-fat diet, averaging 2.86±0.27 L/min during control and 4.45±0.55 L/min during the fifth week of the high-fat diet (Fig 2). Cardiac index (cardiac output/kilogram body weight) did not change significantly, averaging 0.120±0.012 during control and 0.125±0.011 L/min per kilogram body weight during the fifth week of the high-fat diet. The rise in cardiac output was not accompanied by an increase in stroke volume, which averaged 44±4 mL during control and 40±4 mL during the fifth week of fat feeding. Heart rate increased by 57%, averaging 68±5 beats per minute during control and 107±9 beats per minute after 5 weeks of the high-fat diet. Total peripheral vascular resistance decreased significantly, from 30.9±2.1 to 25.0±2.6 mm Hg/L per minute after 5 weeks of fat feeding. However, total peripheral resistance index (arterial pressure/cardiac index) increased approximately 20%, from 712±50 to 854±35 mm Hg/[L/min/kg] after 5 weeks of the high-fat diet.

The high-fat diet was associated with marked sodium and water retention, with urinary sodium excretion averaging 62±10 mmol/d during control and 40 to 50 mmol/d during 5 weeks of the high-fat diet (Fig 3). Therefore, cumulative sodium balance increased progressively to 507±107 mmol above control on the 35th day of the high-fat diet. Urinary chloride excretion also increased significantly during the high-fat diet, averaging 120±13 mmol/d during control and 107±11 mmol/d during the high-fat diet; thus, there was a net chloride retention of approximately 455 mmol during 35 days of the high-fat diet. No significant differences in urinary potassium excretion were measured; however, potassium excretion averaged 54±6 mmol during control and 48±6 mmol during the high-fat diet, and there was a net potassium accumulation of approximately 210 mmol after 5 weeks. Urine volume averaged 799±131 mL/d during control and 577±100 mL/d during 5 weeks of the high-fat diet. In addition, water intake from drinking increased from 126±35 to an average of 352±107 mL/d during the 5 weeks of fat feeding, resulting in a net fluid accumulation of approximately 15.7 L after 35 days of the high-fat diet. This calculation, however, assumes that insensible fluid losses remained constant, an assumption that is probably incorrect because the high-fat diet may have increased metabolic rate. Therefore, the
calculations of net fluid balance in these studies are only approximate values.

GFR increased 17% to 41% above control during the 5 weeks of the high-fat diet; after 5 weeks, GFR averaged 135±4% of control (Fig 4). Similar increases (20% to 66%) in effective renal plasma flow occurred, and after 5 weeks of fat feeding, effective renal plasma flow averaged 149±19% of control. Filtration fraction did not change significantly, averaging 0.34±0.04 during control and 0.33±0.02 after 5 weeks of the high-fat diet. Sodium iothalamate space, an index of extracellular fluid volume, increased 26% to 40% and averaged 131±4% of control after 5 weeks of fat feeding (Fig 5). Thus, sodium iothalamate space increased by approximately 2 to 3 L during 5 weeks of the high-fat diet. The mechanisms responsible for sodium retention were related to increased tubular reabsorption, because total sodium reabsorption increased to 136±5% of control and fractional sodium excretion decreased significantly during the high-fat diet (Fig 6).

Plasma renin activity increased from 0.46±0.12 to 1.10±0.23 ng angiotensin I/mL per hour after 5 weeks of fat feeding, whereas plasma aldosterone concentration did not change significantly (Table 1). Plasma norepinephrine and epinephrine concentrations also did not change significantly, averaging 166±23 and 125±32 pg/mL during control and 206±22 and 106±40 pg/mL, respectively, after 5 weeks of fat feeding. There were no significant changes in hematocrit, plasma sodium concentration, or plasma potassium concentration. However, plasma protein concentration increased from 6.85±0.29 g % during control to 7.57±0.15 g % after 5 weeks of the high-fat diet. Plasma insulin concentration increased almost threefold, from 11.1±2.6 to 30.1±7.0 μU/mL after 5 weeks of the high-fat diet. There was a slight but significant increase in plasma glucose concentration, from 103±10 to 121±9 mg % after 5 weeks of the high-fat diet.

![Graph 2](https://example.com/graph2.png)

Fig 2. Bar graphs show effects of 5 weeks of high-fat diet on heart rate, cardiac output, and total peripheral vascular resistance. Values represent weekly averages obtained from measurements made 18 hours each day. C, average values for 5 control days preceding high-fat diet. Values represent mean±SEM for seven dogs.

![Graph 3](https://example.com/graph3.png)

Fig 3. Plots show effects of high-fat diet for 5 weeks on daily urinary sodium excretion and cumulative sodium balance. Values represent mean±SEM for seven dogs.
**Time-Control Dogs**

There were no major changes in systemic hemodynamics, renal function, or endocrine function in the time-control dogs (Table 2). Mean arterial pressure averaged 90 ± 7 mm Hg during control and 87 ± 5 mm Hg during the 5-week time control. There were also no significant changes in cardiac output, heart rate, or total peripheral resistance in the time-control dogs. Urinary sodium excretion averaged 71 ± 7 mmol/d during the 5-day control period and 73 ± 6 mmol/d during the 5-week time-control period. Thus, there was a slight decrease in cumulative sodium balance of approximately 115 mmol in the time-control dogs, compared with an increase of more than 500 mmol in cumulative sodium balance in obese dogs. There were no significant changes in urinary excretion of potassium or chloride or in urine volume during the 5-week time-control period. Renal hemodynamics remained stable, with GFR averaging 77.9 ± 11.4 mL/min during the initial control period and 78.0 ± 8.1 mL/min during the 5-week time-control period. Effective renal plasma flow also did not change significantly during the 5-week time-control period, and there were no changes in plasma electrolytes, hematocrit, or plasma protein concentration.

**Discussion**

Previous studies indicate that weight gain, even over a period of several weeks, elevates blood pressure in experimental animals and humans. Wood and Cash found that weight gain consistently raised blood pressure in normotensive and hypertensive dogs, regardless of whether they were placed on a high-fat or high-protein diet. Rocchini et al also reported that a high-fat diet for 5 weeks in dogs caused marked weight gain and hypertension and provided considerable evidence that this model mimics the hemodynamic and metabolic changes associated with obesity in humans. For example, obese dogs exhibit hyperinsulinemia, insulin resistance, and glucose intolerance, similar to that found in obese humans. Previous studies by Rocchini et al provided important information about the pathogenesis of weight-related increases in blood pressure in obese dogs. Their observations suggest that obesity is associated with increased cardiac output, possibly in excess of the increased flow to adipose tissue, and that the rise in blood pressure was accompanied by marked sodium and fluid retention. The mechanisms responsible for sodium and fluid retention, however, were not directly assessed in those studies. In the present study, we examined the changes in renal hemodynamics and tubular function responsible for altered sodium handling during a high-fat diet in dogs and quantitated changes in systemic hemodynamics using methods that allowed continuous monitoring of arterial pressure, cardiac output, heart rate, stroke volume, and total peripheral resistance on a beat-by-beat basis, 24 h/d. This information permits a more complete characterization of the hemodynamic abnormalities associated with obesity by including values obtained during periods of normal daily activity as well as in resting conditions.

**Sodium Retention in Obesity**

Previous experimental studies and theoretical analyses suggest that altered renal excretory capability plays a key role in the etiology of experimental and human essential hypertension. Impaired renal excretory capability may be caused by altered renal hemodynamics or by increased tubular reabsorption that can alter pressure natriuresis and increase blood pressure. Studies in humans as well as experimental animals indicate that obesity-induced hypertension is also associated with impaired pressure natriuresis. In the present study, weight gain caused by feeding a high-fat diet increased cumulative sodium balance by more than 500 mmol. The sodium retention appeared to exceed that needed for the additional tissue associated with weight gain, because sodium-iothalamate space, an index of extracellular fluid volume, increased by approximately 35% with obesity. Rocchini et al previously found significant increases in plasma volume in this...
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model, suggesting that obese dogs are somewhat volume expanded. Although the mechanisms responsible for the sodium retention have not been fully elucidated, our results indicate that it is not due to renal vasoconstriction and decreased filtered sodium load. In fact, GFR and filtered sodium load increased markedly, as did renal plasma flow, during the development of obesity. Sodium retention was caused by increased tubular reabsorption, because total sodium reabsorption and fractional sodium reabsorption both increased markedly during the high-fat diet. Thus, obesity-induced hypertension is associated with enhanced tubular reabsorption that may play an important role in shifting pressure natriuresis to higher blood pressures and in causing hypertension.

**Hyperinsulinemia in Obese Dogs**

The mechanisms responsible for increased tubular reabsorption and hypertension in obesity are not entirely clear, but one possible cause is hyperinsulinemia. In the present study, fasting plasma insulin concentration increased twofold to threefold during 5 weeks of the high-fat diet, possibly as a compensation for insulin resistance. Previous studies have shown a positive correlation between blood pressure and plasma insulin in obese dogs and in humans. In addition, several acute studies have shown that insulin reduces sodium excretion, possibly by increasing reabsorption in the loop of Henle. If the antinatriuretic effects of insulin were maintained chronically, this would lead to a shift of renal-pressure natriuresis and eventually an increase in arterial pressure.

Recent studies in our laboratory, however, indicate that chronic hyperinsulinemia, comparable to that found in obese dogs, failed to elevate tubular reabsorption to the extent seen in obese dogs and did not cause hypertension. In fact, hyperinsulinemia tended to lower blood pressure, and most of the long-term antinatriuretic effect of insulin appeared to be secondary to the fall in blood pressure rather than a direct action of insulin on the kidney. Chronic insulin infusion for 4 weeks also did not elevate blood pressure in dogs with reduced kidney mass and maintained on a high-sodium intake or in dogs infused with norepinephrine or angiotensin II. Although these studies do not support the concept that hyperinsulinemia plays a major role in obesity-induced hypertension in dogs, they do not rule out the possibility that insulin might exert effects on blood pressure that are very slow to develop and are not revealed over a period of several weeks. Nevertheless, these observations suggest that hyperinsulinemia per se cannot explain the development of hypertension over a period of 5 weeks in obese dogs, as found in the present study.

**Renin-Angiotensin System in Obese Dogs**

Another possible explanation for increased tubular reabsorption and hypertension in obese dogs is activation of the renin-angiotensin system. Previous studies have shown that even small increases in angiotensin II levels can increase blood pressure, especially when associated with volume expansion. In the present study, plasma renin activity increased more than twofold despite marked expansion of extracellular fluid

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**Table 1. Effects of High-Fat Diet in Dogs**

<table>
<thead>
<tr>
<th>Time</th>
<th>PINS (µU/mL)</th>
<th>PGLU (mg %)</th>
<th>PRA (ng Ang I/100 mL/h)</th>
<th>Aldosterone (ng/dl)</th>
<th>Serum norepinephrine (pg/mL)</th>
<th>Serum epinephrine (pg/mL)</th>
<th>Hematocrit (%)</th>
<th>PNa (mmol/L)</th>
<th>PK (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11.1±2.6</td>
<td>103±10</td>
<td>0.46±0.12</td>
<td>2.7±0.2</td>
<td>166±27</td>
<td>125±32</td>
<td>0.36±0.02</td>
<td>6.85±0.29</td>
<td>147.1±8.3</td>
</tr>
<tr>
<td>Week 1</td>
<td>15.0±1.8*</td>
<td>93±13</td>
<td>0.90±0.25</td>
<td>3.8±0.6</td>
<td>193±36</td>
<td>58±17*</td>
<td>0.35±0.02</td>
<td>6.73±0.28</td>
<td>147.8±1.0</td>
</tr>
<tr>
<td>Week 2</td>
<td>19.0±4.0*</td>
<td>103±13</td>
<td>0.96±0.28</td>
<td>3.3±0.6</td>
<td>145±10</td>
<td>79±19</td>
<td>0.35±0.02</td>
<td>7.17±0.20*</td>
<td>148.7±0.5</td>
</tr>
<tr>
<td>Week 3</td>
<td>38.5±12.3*</td>
<td>119±3*</td>
<td>0.73±0.14</td>
<td>3.1±0.4</td>
<td>178±33</td>
<td>97±22</td>
<td>0.37±0.02</td>
<td>7.62±0.24*</td>
<td>149.6±0.4</td>
</tr>
<tr>
<td>Week 4</td>
<td>39.7±10.7*</td>
<td>123±9*</td>
<td>0.88±0.25*</td>
<td>3.6±0.5</td>
<td>248±49</td>
<td>132±37</td>
<td>0.38±0.02</td>
<td>7.62±0.18*</td>
<td>147.2±0.6</td>
</tr>
<tr>
<td>Week 5</td>
<td>30.1±7.0*</td>
<td>121±9*</td>
<td>1.10±0.23*</td>
<td>3.7±0.8</td>
<td>206±22</td>
<td>106±40</td>
<td>0.37±0.03</td>
<td>7.57±0.15*</td>
<td>149.2±0.5</td>
</tr>
</tbody>
</table>

*P<.05 compared with control.

**Table 2. Time-Control Dogs**

<table>
<thead>
<tr>
<th>Time control</th>
<th>Body weight (kg)</th>
<th>MAP (mm Hg)</th>
<th>CO (L/min)</th>
<th>HR (bpm)</th>
<th>TPR (mm Hg/L/min)</th>
<th>UNaV (mEq/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>23.3±0.7</td>
<td>90±7</td>
<td>3.39±0.19</td>
<td>64±4</td>
<td>28.7±1.0</td>
<td>71±6.7</td>
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<td>Time control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>23.0±0.8</td>
<td>89±6</td>
<td>3.43±0.18</td>
<td>66±6</td>
<td>27.0±0.7</td>
<td>75±5.2</td>
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<tr>
<td>Week 2</td>
<td>23.2±1.1</td>
<td>87±7</td>
<td>3.20±0.13</td>
<td>63±5</td>
<td>28.1±1.9</td>
<td>69±5.8</td>
</tr>
<tr>
<td>Week 3</td>
<td>23.1±0.9</td>
<td>89±6</td>
<td>3.36±0.20</td>
<td>74±10</td>
<td>27.6±1.5</td>
<td>74±7.3</td>
</tr>
<tr>
<td>Week 4</td>
<td>23.3±0.6</td>
<td>88±4</td>
<td>3.42±0.18</td>
<td>75±7</td>
<td>26.5±1.1</td>
<td>75±3.1</td>
</tr>
<tr>
<td>Week 5</td>
<td>24.0±0.6</td>
<td>87±5</td>
<td>3.13±0.14</td>
<td>74±9</td>
<td>28.8±1.3</td>
<td>70±6.1</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; TPR, total peripheral vascular resistance; UNaV, urinary sodium excretion. Values are mean±SEM for four dogs and represent weekly averages obtained from daily averages.
volume. Previous studies of the renin-angiotensin system in obesity have yielded conflicting results. Rocchini et al. found no change in plasma renin activity in obese dogs, whereas Tuck et al. reported that plasma renin activity was elevated in obese humans. In our studies, plasma renin activity was elevated more than twofold after 5 weeks of the high-fat diet despite marked sodium retention and increased extracellular fluid volume. The inability to suppress angiotensin II levels appropriately during volume expansion may cause blood pressure to be very sodium sensitive, leading to a decreased slope of pressure natriuresis. This observation is consistent with the observation that blood pressure is salt sensitive in obese subjects. However, the contribution of increased angiotensin II formation to salt sensitivity of blood pressure in obese dogs or humans has not been fully elucidated.

### Sympathetic Nervous System in Obesity

A third mechanism that could contribute to increased tubular reabsorption, altered pressure natriuresis, and hypertension in obesity is increased sympathetic activity. Increased caloric intake appears to stimulate sympathetic activity, as assessed by norepinephrine turnover in peripheral tissues. Plasma norepinephrine levels and the norepinephrine response to various stimuli such as upright posture and isometric handgrip may also be elevated in obese subjects. Rocchini et al. have also reported that plasma norepinephrine concentration is elevated in obese hypertensive dogs. In the present study, plasma norepinephrine concentrations tended to increase during 5 weeks of the high-fat diet, but the changes were not statistically significant. However, plasma norepinephrine concentration may not be a very sensitive index of sympathetic activity.

Consistent with the possibility that sympathetic activity may be increased in obese dogs, we found marked increases in heart rate during 5 weeks of the high-fat diet. However, increased heart rate could signify increased activity of the cardiac sympathetic nerves, withdrawal of parasympathetic tone, or an increase in the intrinsic rate of the heart. In support of the possibility that increased sympathetic activity may contribute to obesity-induced hypertension, preliminary studies indicate that combined α- and β-adrenergic blockade for 7 days reduced arterial pressure to a much greater extent in obese than in normal dogs. However, the contribution of increased sympathetic activity to stimulation of tubular reabsorption, altered pressure natriuresis, and hypertension in obese dogs has not been determined.

### Renal Vasodilation in Obesity

Accompanying increased tubular reabsorption in obesity was marked renal vasodilation, increased renal plasma flow, and elevated GFR. These changes obviously cannot be accounted for by increased sympathetic activity or activation of the renin-angiotensin system, because activation of these systems would tend to decrease rather than raise renal plasma flow and GFR. However, the fact that GFR increased in obese dogs is not incompatible with the possibility that activation of the renin-angiotensin and sympathetic systems may have contributed to increased reabsorption and hypertension. It is possible that modest increases in angiotensin II levels and sympathetic activity, insufficient to cause renal vasoconstriction, could contribute to increased tubular reabsorption in this model. Previous studies have shown that moderate stimulation of renal nerves and low-dose angiotensin II infusion can increase renal tubular reabsorption without altering renal blood flow or GFR.

Although the cause of increased renal plasma flow and GFR associated with obesity is unclear, one possibility that should be considered is that increased GFR may be a compensatory response to increased tubular reabsorption. Increased tubular reabsorption would tend to reduce urinary sodium excretion, thereby necessitating either an increase in filtered sodium load or a compensatory decrease in tubular reabsorption to maintain sodium balance. If increased reabsorption occurred at a site prior to the macula densa (eg, proximal tubule or loop of Henle), the rise in GFR and renal plasma flow could occur via a macula densa mechanism; increased reabsorption prior to the macula densa would decrease distal tubular sodium chloride delivery, thereby initiating a macula densa feedback-mediated vasodilation of afferent arterioles and a compensatory increase in GFR and filtered sodium load. A macula densa feedback mechanism could also explain the increased plasma renin activity associated with obesity, because decreased sodium chloride delivery to the macula densa would tend to stimulate renin secretion. However, it should be emphasized that our experiments were not designed to directly test this hypothesis and the explanation provided above must be considered speculative.

### Systemic Hemodynamics in Obese Dogs

Another important observation of our studies is that obesity is associated with marked increases in cardiac output, as assessed by beat-by-beat measurements made 24 h/d. Previous studies by Rocchini et al. also suggest that obesity is associated with increased cardiac output. However, when cardiac output is expressed per unit body weight (cardiac index), there were no significant changes associated with the high-fat diet. Yet normalization for body weight may not be appropriate in our experiments, because much of the weight gain may be related to an increase in adipose tissue, which has relatively low blood flow compared with some other tissues. Thus, obesity may be associated with an increased blood flow in nonadipose tissue. In support of this possibility, we found in the present study that renal blood flow was markedly increased in obese dogs, and Rocchini et al. also reported that blood flows in other tissues, such as gastrointestinal, heart, and brain, were elevated in obese compared with normal dogs. Moreover, blood flow in the forearm (mainly skeletal muscle and skin) is greater in obese than nonobese subjects. Preliminary studies from our laboratory suggest that this vasodilation in obese dogs cannot be explained entirely by enhanced endothelium-derived nitric oxide synthesis. However, the mechanisms responsible for regional vasodilation in obesity are still unclear, and further studies are therefore needed to more fully explore other possible mechanisms.

In summary, the results of the present study indicate that marked sodium and water retention associated with obesity-induced hypertension are due to increased tubular reabsorption rather than renal vasoconstriction.
Increased reabsorption may be compensated, in part, by renal vasodilatation, increased GFR, and increased filtered load of water and electrolytes. The mechanisms responsible for increased tubular reabsorption are still unclear, although enhanced activity of the renin-angiotensin and sympathetic nervous systems are likely candidates. Because weight gain appears to be one of the most important factors in contributing to increased blood pressure in many essential hypertensive individuals, further study of the mechanisms responsible for obesity-induced hypertension is needed.

Acknowledgments

Supported by grants HL-11678, HL-23502, and HL-39399 from the National Institutes of Health, Bethesda, Md. We thank Calvin T. Chadwick and Beth Miller for excellent technical assistance and Drs Thomas Lohmeier and Glen Reinhardt for conducting the catecholamine assays. We also greatly appreciate the assistance of Mrs Ivadelle Heidke in preparing the manuscript.

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Hypertension. 1993;22:292-299
doi: 10.1161/01.HYP.22.3.292

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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