Obesity-Induced Hypertension in the Dog

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SUMMARY To study the relationship between body weight and blood pressure, we have developed an animal model of obesity-induced hypertension. Nine adult mongrel dogs were chronically instrumented with aortic and vena caval catheters. After a 2-week control period, all dogs were made to gain weight by adding 2 lb/day of beef fat to their diet for 5 weeks. Blood pressure, heart rate, and body weight were measured daily before the addition of dietary fat, during the 5 weeks of the high fat diet, and for 6 weeks after the fat supplement was stopped. Plasma volume and cardiac output were measured prior to and after 5 weeks of the fat diet. During the 5-week high fat diet, the dogs' body weight increased from 22.2 ± 2.1 to 27.4 ± 3 kg (p<0.001); mean blood pressure increased from 90 ± 5 to 112 ± 6 mm Hg (p<0.01); and heart rate increased from 70 ± 7 to 85 ± 5 beats/min (p<0.05). Blood pressure, heart rate, and body weight returned to near control values after the fat diet was stopped. Over the 5-week fat diet, the dogs' plasma volume increased from 920 ± 130 to 1059 ± 195 ml (p<0.05); cardiac output increased from 2.5 ± 0.4 to 3.1 ± 0.3 L/min (p<0.05); and systemic vascular resistance increased from 35.3 ± 8 to 38.9 ± 9 mm Hg/L/min (p<0.1). Weight gain in the dogs was also associated with hyperinsulinemia and insulin resistance. Our findings have demonstrated that weight gain in the dog is associated with an increase in heart rate, blood pressure, cardiac output, plasma volume, and fasting insulin concentration, and we think that our animal model should be ideal for studying the pathogenesis of obesity-induced hypertension.

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Key Words • obesity • hypertension • hyperinsulinemia

SINCE 1924, it has been known that body weight and arterial pressure are related.1 Despite the strong association between obesity and hypertension, little is known about the mechanism of this association.2,3 The lack of knowledge about the pathogenesis of obesity-induced hypertension is not surprising, since few animal models have been developed for its study. In 1939, Wood and Cash1 first reported that dogs with and without renal hypertension developed a marked increase in systolic blood pressure when caused to gain weight by a diet composed chiefly of beef fat. Since that report, little new information has been published either to validate this model of obesity-associated hypertension or to study its pathophysiologic basis. The purpose of this report is to describe our experience with a dog model of obesity-induced hypertension similar to that described by Wood and Cash. In addition, we have attempted to characterize the hemodynamic effects associated with weight gain in the dog and to demonstrate that the dog is an appropriate model in which to study the etiology of obesity-associated hypertension in humans.

Methods

Nine adult mongrel dogs (four males and five females) were trained to lie quietly on a padded table. All dogs were then surgically instrumented with an ascending aorta catheter and a right atrial catheter. After surgery, the dogs were allowed to recover for 2 weeks before baseline measurements were made. After 2 weeks of baseline measurements of arterial pressure, heart rate, and body weight, the dogs were made to gain weight by feedings of 2 lb of cooked beef fat per day in addition to their regular diet of one can of dog food (Ken-L-Ration). The fat was freshly cooked and mixed into the dogs' daily food for 5 weeks. All dogs were fed between the hours of 1300 and 1500 each day. After 5 weeks, the fat was discontinued and the dogs were fed their regular diet for an additional 6 weeks. Blood pressure, heart rate, body weight, and fasting insulin concentration were measured daily. Cardiac output and plasma volume were measured in...
triplicate on two separate days during both the baseline period and the fifth week of the high fat diet. Glucose tolerance was measured in all dogs (before weight gain, after 5 weeks of the high fat diet, and 6 weeks after the normal diet was resumed) by giving each dog glucose (1 g/kg of body weight) via the right atrial catheter. Plasma glucose and insulin were measured prior to and after 30, 60, 90, and 120 minutes of intravenous administration of glucose. All measurements were made between 0800 and 1100 and before the daily feeding (the dogs having not been fed since 1700 the previous day). All the procedures in this study were in accordance with the University of Michigan guidelines on animal experimentation.

**Laboratory Measurements**

Arterial pressure was measured with P23Db Statham pressure transducers (Statham, Oxnard, CA, USA) and recorded on a VR6 optical recorder (Electronics for Medicine, White Plains, NY, USA). Cardiac output was measured with cardiogreen dye, using a green-dye cardiac-output computer (Waters Instrument, Rochester, MN, USA). Plasma volume was measured using Evans blue dye, plasma glucose was measured by the glucose oxidase method, and insulin was measured by radioimmunoassay.

**Statistical Analysis**

All values are means ± SE. Statistical analysis of mean glucose and insulin levels over time and between interventions (before the high fat diet, after 5 weeks of the high fat diet, and 6 weeks after the high fat diet was stopped) were performed using a repeated measures analysis of variance. Weekly blood pressures, heart rates, and body weights were determined by averaging the daily values for each week. Repeated-measures analysis was then used to determine whether a significant change in blood pressure, heart rate, or body weight had occurred during and after the high fat diet. Student’s t test for paired observations was used to determine if a significant change (p < 0.05) occurred. Regression analysis was used to express the relationship between change in mean arterial pressure and change in body weight divided by initial weight.

**Results**

Over the 5 weeks of the high fat diet, all of the dogs’ body weights progressively increased from 22.2 ± 2.1 kg to 27.4 ± 3 kg after 5 weeks of the high fat diet (p < 0.001; Figure 1). In addition, all the dogs appeared to have gained weight, especially around the neck, chest, and abdomen. Seven of the nine dogs experienced a significant increase in systolic, diastolic, and mean blood pressure during the 5 weeks of the high fat diet. As the dogs gained weight, all nine demonstrated a progressive increase in arterial pressure (systolic 128 ± 5, diastolic 74 ± 6, and mean 90 ± 5 mm Hg pre–high fat diet, and systolic 171 ± 8, diastolic 83 ± 5, and mean 112 ± 6 mm Hg after 5 weeks of the high fat diet; p < 0.01; see Figure 1). In addition to the temporary relationship between weight gain and increase in arterial pressure, we observed that there was a significant linear correlation between the change in body weight divided by initial body weight and the change in mean arterial pressure (r = 0.72, p < 0.01). Heart rate progressively increased as the dogs gained weight (70 ± 7 beats/min pre–high fat diet and 85 ± 5 beats/min after 5 weeks of the high fat diet, p < 0.01). With cessation of the high fat diet, there was a progressive decrease in body weight, arterial pressure, and heart rate to baseline values (see Figure 1). In addition to measuring the change in blood pressure and heart rate that occurred with weight gain, we also measured plasma volume and cardiac output before and after 5 weeks of the high fat diet (Figure 2). Plasma volume increased from 920 ± 130 to...

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**Figure 1.** Changes in body weight, mean arterial pressure (MAP), and heart rate (HR; in beats/min) in nine dogs fed a high fat diet for 5 weeks. Data points represent means ± SE. Stars indicate a significant (p < 0.05) change.

**Figure 2.** Cardiac output (CO), systemic vascular resistance (SVR) and plasma volume (PV) before and after 5 weeks of a high fat diet. Values indexed for body weight are depicted in graphs on the right.
1059 ± 195 ml (p<0.05). However, when plasma volume was indexed for body weight, we observed no change in plasma volume with weight gain. Similarly, we observed a significant increase in cardiac output with weight gain (2.5 ± 0.4 to 3.1 ± 0.3 L/min, p<0.05) and a small but not statistically significant increase in total systemic vascular resistance (35.3 ± 8 to 38.9 ± 9 mmHg/L/min, p<0.1). As with plasma volume, when cardiac output was indexed for body weight, the increase in cardiac output was no longer significant; however, when indexed to body weight, total systemic vascular resistance significantly increased (p<0.05).

Because hyperinsulinemia and glucose intolerance are frequent findings in human obesity, we evaluated glucose tolerance in our dog model before the high fat diet, after 5 weeks of the high fat diet, and 6 weeks after stopping the high fat diet. After 5 weeks of the high fat diet, the dogs developed an abnormal response to an intravenous glucose tolerance test (Figure 3). After 5 weeks of the high fat diet, plasma glucose concentration was significantly increased at 1 and 2 hours after intravenous glucose administration (p<0.05). Even more dramatic changes were observed in the insulin response. Fasting insulin and all insulin values after intravenous glucose administration were significantly increased after 5 weeks of the high fat diet (p<0.05). Six weeks after the high fat diet was stopped, both the glucose and insulin responses to the intravenous glucose tolerance test returned to baseline values. In addition, we observed that during the high fat diet, there was a temporal relationship between fasting plasma insulin concentration and mean arterial pressure (Figure 4).

Discussion

Although there are a number of epidemiological studies that suggest a strong association between obesity and hypertension,9-10 the pathological basis for the hypertension is poorly understood. To a large extent this lack of knowledge is related to the fact that no animal models of obesity-induced hypertension have been developed. In the present study, we have documented that dogs that are fed a high fat diet will gain weight and that this weight is temporally associated with an increase in arterial pressure. Although it is possible that the high fat diet itself, possibly through its fatty acid composition could have been responsible for the observed increase in blood pressure,11 we do not believe this to be the case. Rather, we believe that the following two observations suggest that the increase observed in arterial pressure was directly related to increased body weight. The first observation is our finding of a significant correlation between the percent increase in body weight and the change in arterial pressure. In addition, with the cessation of the high fat diet, both body weight and arterial pressure gradually returned to baseline values. The second observation was made by Wood and Cash, who reported that in two dogs whose weight was maintained by a diet of raw beef, no change in blood pressure occurred. However, when the two dogs were fed enough raw beef to cause marked weight gain, Wood and Cash observed that both systolic and diastolic blood pressures increased.4

We noted, as did Wood and Cash,4 that weight gain in the dogs resulted in a greater increase in systolic pressure than in diastolic pressure (p<0.05). The predominant increase in systolic blood pressure and a concomitant increase in heart rate suggest that weight...
gain in the dog may be associated with increased sympathetic nervous system activity. Based on findings of increased plasma norepinephrine levels, others have suggested that increased sympathetic activity may contribute to the increased blood pressure observed in human obesity. In addition, weight reduction has been reported to result in a progressive decrease in both plasma and urine catecholamines and in blood pressure. Therefore, it is possible that weight gain and loss in the dog also alter sympathetic nervous system activity.

In addition to increasing arterial pressure and heart rate, weight gain in our dogs was associated with other hemodynamic changes. With weight gain, both plasma volume and cardiac output significantly increased ($p < 0.05$), and there was a small but not significant increase in systemic vascular resistance. However, when these variables were indexed to body weight, we no longer observed a significant increase in either plasma volume or cardiac output, but we did observe an increase in weight-indexed systemic vascular resistance. Similar findings have been reported for obesity in humans. Although it is generally accepted that, when compared to lean subjects, obese subjects experience increased cardiac output and blood volume, when these values are indexed for either body surface or body weight, the differences between lean and obese individuals disappear. However, is normalization for size appropriate? Lesser and Deutsch have suggested that in obese individuals cardiac output is probably disproportionately large for the amount of adipose tissue mass, thus suggesting that blood flow to nonadipose tissue may be increased. Further studies in our dogs during weight gain may enable us to determine whether regional blood flow is altered during the development of obesity.

Human obesity is associated with both hemodynamic and metabolic changes. Hyperinsulinemia, insulin resistance, and glucose intolerance are frequent findings in human obesity. We observed that weight gain in the dog was also associated with a progressive increase in fasting insulin concentration. In addition, after 5 weeks of the high fat diet, the higher plasma insulin levels that occurred at every time point following the intravenous administration of glucose suggested that the dogs had become insulin resistant. Furthermore, we observed that the increase in blood pressure that was associated with weight gain in the dog also appeared to be temporally related to the increase in fasting plasma insulin concentration. Lucus and coworkers recently demonstrated a significant relationship between fasting serum insulin level and blood pressure in obese women. In the dog, as in humans, hyperinsulinemia may be important in the regulation of blood pressure during and after weight gain.

Although there are a number of similarities between obesity in our dog model and human obesity, there are also some differences. First, in obese humans, total peripheral resistance remains normal, and the increase in arterial pressure is mediated by an increase in cardiac output due to an expanded stroke volume with little or no change in heart rate. In contrast, in the present dog model we observed a distinct increase in heart rate and also a slight increase in peripheral resistance. We believe that the discrepancy between our dog model and human obesity may in large part be due to the fact that the dogs were being overfed and thus were in an anabolic state rather than the more eumetabolic state of human obesity. Had we studied our dogs over a longer period of time and at a constant weight, it is likely that the increase in heart rate would have returned to control values. Finally, in human obesity the excess weight is predominantly due to an increase in fat mass. Because we did not measure body composition in our dogs, we do not know if the weight gain we observed was due solely to an increase in fat mass or to an increase of fat and lean mass combined. In future studies, we hope to be able to determine the tissue composition of the weight gained.

In summary, weight gain in the dog, as in humans, is associated with elevations in blood pressure, heart rate, plasma volume, cardiac output, and fasting insulin concentration. Our data suggest that dogs fed a high fat diet may be good models in which to study the pathogeneses of obesity-induced hypertension in humans.

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