Prolonged Activation of the Baroreflex Abolishes Obesity-Induced Hypertension

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Abstract—Prolonged electrical activation of the carotid baroreflex produces sustained reductions in sympathetic activity and arterial pressure in normotensive dogs. The main goal of this study was to assess the influence of prolonged baroreflex activation on arterial pressure and neurohormonal responses in 6 dogs with obesity-induced hypertension. After control measurements, the diet was supplemented with cooked beef fat for 6 weeks, whereas sodium intake was held constant. After 4 weeks of the high-fat diet, there were increments in body weight from 25.8 ± 0.7 to 38.6 ± 1.0 kg, mean arterial pressure from 97 ± 2 to 110 ± 3 mm Hg, heart rate from 67 ± 3 to 91 ± 4 bpm, and plasma norepinephrine concentration from 141 ± 35 to 280 ± 52 pg/mL. Plasma glucose and insulin concentrations were elevated, but increases in plasma renin activity during the initial weeks of the high-fat diet were not sustained. During week 5, baroreflex activation resulted in sustained reductions in mean arterial pressure, heart rate, and plasma norepinephrine concentration; at the end of week 5, these values were 87 ± 2 mm Hg, 77 ± 4 bpm, and 166 ± 45 pg/mL, respectively. These suppressed values returned to week 4 levels during a 7-day recovery period after baroreflex activation. There were no changes in plasma glucose or insulin concentrations, or plasma renin activity during prolonged baroreflex activation. These findings indicate that baroreflex activation can chronically suppress the sympathoexcitation associated with obesity and abolish the attendant hypertension while having no effect on hyperinsulinemia or hyperglycemia.

Key Words: baroreflex ■ hypertension ■ heart rate ■ obesity ■ sympathetic nervous system ■ norepinephrine ■ renin–angiotensin system

Although obesity is a major risk factor for the development of hypertension, the mechanisms whereby obesity contributes to hypertension are not completely understood. Obesity is characterized by activation of the sympathetic nervous system, and there is considerable evidence that the sympathetic nervous system plays an important role in the development of hypertension.1–11 However, despite years of investigation, the precise causal mechanisms contributing to sympathetic activation in obesity hypertension are unclear. Proposed mechanisms for stimulation of the sympathetic nervous system in obesity include hyperinsulinemia, hyperleptinemia, increased circulating levels of angiotensin II (Ang II), obstructive sleep apnea, and baroreflex dysfunction.1–5,7

The baroreflex plays a critical role in acute regulation of arterial pressure, but its importance in long-term control of sympathetic activity and arterial pressure is controversial.13–15 For years, the dogma has been that the baroreflex is relatively unimportant in long-term control of arterial pressure, because it resets to the prevailing level of arterial pressure and, therefore, must lack the ability to chronically alter sympathetic activity and arterial pressure. Contrary to this view, recent studies using novel approaches in chronically instrumented animals suggest that baroreflex resetting is incomplete in hypertension and that baroreflex suppression of sympathetic activity is a sustained response that may serve as a compensatory mechanism to attenuate the severity of hypertension.13–22 Because these studies indicate that baroreflexes do chronically influence the prevailing level of sympathetic activity, they lend credence to the hypothesis that baroreflex dysfunction could contribute significantly to chronic sympathetic activation in obesity hypertension.5–7 However, this possibility depends on the capacity of the baroreflex to chronically suppress sympathetic activity and lower arterial pressure in obesity hypertension, a quantitative assessment that has not been made to date.

We recently developed technology to evaluate the time dependency, the underlying mechanisms, and the conditions that impact the magnitude of the blood pressure–lowering effects of the baroreflex.23,24 To activate the baroreflex, an externally adjustable pulse generator is used to electrically stimulate electrodes chronically implanted around both
carotid sinuses of dogs. In normotensive dogs, pronounced and sustained reductions in mean arterial pressure (MAP) occurred in response to prolonged baroreflex activation (PBA). In light of these observations, we hypothesized that baroreflex activation might be efficacious in attenuating hypertension induced by obesity. This hypothesis was based on studies indicating that the renal nerves play an important role in mediating obesity hypertension and that activation of the baroreflex has sustained effects to suppress renal sympathetic nerve activity and promote sodium excretion. Thus, the main goal of the present study was to test this hypothesis and to gain insight into the mechanisms that might account for the favorable cardiovascular effects of PBA in obesity hypertension. In addition, because the insulin resistance and hyperinsulinemia of obesity has been postulated to be a secondary response to neural effects of PBA in obesity hypertension. In addition, because the insulin resistance and hyperinsulinemia of obesity has been postulated to be a secondary response to neural mediated reductions in skeletal muscle blood flow that impair glucose uptake, an additional objective of this study was to determine whether sustained inhibition of sympathetic activity by baroreflex activation would have metabolically favorable effects to reduce high circulating levels of insulin and glucose in dogs with obesity-induced hypertension.

Methods

Animal Preparation
All of the procedures were performed in accordance with National Institutes of Health guidelines and approved by the Institutional Animal Care and Use Committee. Surgical procedures were performed under isoflurane anesthesia (1.5% to 2.0%) after premedication with acepromazine (0.15 mg/kg, SC) and induction with thiopental (10 mg/kg, SC).

Six male dogs weighing 23 to 27 kg were used in this study. Arterial and venous catheters were implanted for continuous measurement of arterial pressure and blood sampling and for continuous intravenous infusion of isotonic saline as described previously. In addition, stimulating electrodes were implanted around each carotid sinus, and the lead bodies were connected to a pulse generator. The electrodes and the pulse generator were provided by CVRx, Inc.

Experimental Protocol
During a 3-week postoperative period and throughout the study, the dogs were maintained in metabolic cages, given free access to water, and fed a fixed daily diet of two 15.5-oz cans of prescription heart diet (Hill’s Pet Products) supplemented with 5 mL of vitamin syrup. Two cans of prescription heart diet provide ~5 mmol of sodium and ~55 mmol of potassium. The dogs received a continuous intravenous infusion of isotonic saline at a rate of 350 mL per day, providing a total daily sodium intake of ~60 mmol throughout the study. Water consumption was monitored daily, and 24-hour urine samples were collected at 11:00 AM each day at the time of feeding.

At the end of the second postoperative week, the carotid baroreflex was electrically activated for 48 hours using stimulation parameters described previously. This was done to test the integrity of the carotid sinus implants. Three weeks postoperatively, when steady-state conditions were achieved, control measurements were made. Then, cooked beef fat was added to the regular diet for the next 6 weeks. During the initial 3 to 4 weeks, the diet was supplemented with 0.45 to 0.90 kg per day of fat until body weight increased to ~150% of control. Once this increase in body weight was achieved, during week 4, dietary fat was reduced to ~0.2 kg per day to maintain a constant body weight for the remainder of the 6-week period. This reduction in fat intake commenced at least 48 hours before week 5. During week 5, the carotid baroreflex was electrically activated as described above. A 7-day recovery period followed baroreflex activation.

On intermittent days throughout the control and experimental periods, blood samples (~10 mL) were taken from 1 of the 2 arterial catheters while the dogs were recumbent and in a resting state. Blood samples were analyzed for hematocrit, plasma renin activity (PRA), and the plasma concentrations of sodium, potassium, protein, aldosterone, cortisol, insulin, and norepinephrine (NE).

Analytical Methods
The plasma levels of hormones and NE were measured by radioimmunoassay and high-performance liquid chromatography with electrochemical detection (Agilent 1100), respectively, as described previously. Plasma glucose concentration was measured with the glucose oxidation method (Beckman glucose analyzer 2). Standard techniques were used to measure hematocrit and the plasma concentrations of sodium, potassium, and protein.

Arterial pressure and heart rate were monitored continuously, 24 hours per day, from an arterial catheter. The daily hemodynamic values presented were averaged from the 24-hour period extending from 11:30 AM to 7:30 AM. The hours excluded from the 24-hour analysis included the time required for flushing catheters, calibrating pressure transducers, feeding, and cleaning cages.

Statistical Analysis
Results are expressed as mean±SE. A 1-way ANOVA was used to compare experimental responses to either control or week 4 (last 2 days) of the high-fat diet. Significant differences were established using Dunnett’s t test for multiple comparisons. Statistical significance was considered to be P<0.05.

Results

Hemodynamics, Body Weight, and Urinary Electrolyte Excretion
As illustrated in Figure 1, during the first 4 weeks of the high-fat diet, MAP and body weight increased in parallel with increases reaching statistical significance after 1 week of the high-fat diet. At the end of week 4 of the high-fat diet, MAP increased from a control value of 97±2 to 110±3 mm Hg. During this time, body weight increased ~50% from a control value of 25.8±0.7 to 38.6±1.0 kg and remained at this level for the last 2 weeks of the study. Heart rate also increased throughout the initial 4 weeks of the high-fat diet, and at the end of week 4, heart rate was 91±4 compared with a control value of 67±3 bpm. The induction of hypertension by fat feeding was associated with sodium retention. During the control period, sodium and potassium excretion was 55±2 and 48±3 mmol per day, reflecting the intake of these electrolytes, whereas sodium excretion averaged 45±3 mmol per day during the initial 4 weeks of the high-fat diet. Thus, over the initial 4 weeks of the high-fat diet, there was an average total retention of ~300 mmol of sodium. There was no significant change in potassium excretion during the high-fat diet.

The daily changes in MAP and heart rate in response to PBA during week 5 of the high-fat diet are illustrated in Figure 2. After baroreflex activation, there was an abrupt fall in MAP, averaging ~20 mm Hg over the initial 20 minutes of stimulation. The acute temporal changes in MAP in response to baroreflex activation were similar to those illustrated in an actual polygraph tracing from a previous study. For day 1 of PBA, MAP decreased 18±3 mm Hg, but there was little or no decrease in heart rate. Throughout the remaining 6 days of
PBA, both MAP and heart rate decreased further from week 4 values, falling by 23/110 mm Hg (to 87/102 mm Hg) and 14/11 bpm (to 77/44 bpm) by the end of the 7-day period of PBA. Thus, PBA completely abolished the hypertension induced by the high-fat diet and actually caused MAP to fall to below control levels. PBA also substantially attenuated the tachycardia associated with weight gain, but on the last day of baroreflex activation, heart rate was still 10 bpm higher than before feeding the high-fat diet. More specifically, PBA abolished 60% of the obesity-induced increase in heart rate. After PBA, MAP returned to week 4 hypertensive levels within 24 hours, whereas the restitution of heart rate to week 4 levels took several days longer. A final point is that after 48 hours of baroreflex activation, the fall in MAP (19/2 mm Hg) was virtually identical to the response observed before fat feeding (19/1 mm Hg), which was determined 2 weeks postoperatively.

The daily changes in sodium excretion during PBA are illustrated in Figure 3 and are compared with those reported previously in dogs studied before and after the induction of Ang II hypertension. A notable difference was the absence of sodium retention on day 1 of baroreflex activation in obese compared with normotensive dogs and dogs with Ang II hypertension. In addition, there were no significant changes in potassium excretion during PBA and no significant changes in either sodium or potassium excretion during the recovery period (week 6).

**Figure 1.** Effects of a high-fat diet and prolonged baroreflex activation on MAP, heart rate, and body weight. Values are mean±SEM (n=6). *P*<0.05 vs control.

**Figure 2.** Daily effects of prolonged baroreflex activation on MAP, heart rate, and plasma NE concentration in dogs with obesity hypertension. Values are mean±SEM (n=6). *P*<0.05 vs days 27 to 28 of the high-fat diet.

**Neurohormonal Profile**

Neurohormonal responses during the 6 weeks of the high-fat diet are illustrated in Figure 4 and the Table. During the first 4 weeks of the high-fat diet, there was a progressive increase in plasma NE concentration, which achieved statistical significance by week 3 of the high-fat diet (Figure 4). After 4 weeks of the high-fat diet, plasma NE concentration increased 2-fold from a control level of 141/35 to 280/52 pg/mL. PRA increased substantially during the first 2 weeks of the high-fat diet but returned to control levels as the hypertension progressed (Figure 4). During the initial 2 weeks of the high-fat diet when PRA was elevated, plasma aldosterone concentration also tended to increase above a control level of 4.0/0.5 ng/dL. However, because plasma levels of aldosterone failed to increase in 1 dog (the dog with the highest control level of aldosterone=6.4 ng/dL), changes in plasma aldosterone concentration did not achieve statistical significance during this time or at any time during the high-fat diet (Table). Plasma cortisol concentration increased 2-fold above a control level of 1.4±0.1 µg/dL during weeks 2 and 3 before returning to control thereafter (Table). Plasma insulin concentration doubled in the first week of the high-fat diet and increased progressively during weeks 3 through 6 from a control level of 7.5±0.9 to 33.4±6.7 µU/mL after week 6 of the high-fat diet.

By day 1 of baroreflex activation (day 29), plasma NE concentration decreased to control levels from the elevated values observed at week 4 (Figure 2). Furthermore, plasma
NE remained at this suppressed level throughout the entire week of PBA. After PBA was terminated (day 36), plasma NE concentration increased back to week 4 levels and remained elevated throughout the duration of the high-fat diet. In addition, despite the marked decrease in MAP, PRA did not increase during PBA and remained at week 4 values throughout the 7 days of PBA (Figure 4). Compared with week 4 values, there were no significant changes in the concentrations of aldosterone, cortisol, or insulin during either PBA or the week after PBA.

**Hematocrit and Plasma Concentrations of Electrolytes, Glucose, and Protein**

After the first 2 weeks of the high-fat diet, plasma glucose concentration increased modestly above control levels, despite substantial hyperinsulinemia (Table). PBA had no effect on plasma levels of glucose. Consequently, because insulin concentration was also unaffected by PBA, it would appear that baroreflex suppression of sympathetic activity did not ameliorate insulin resistance during the high-fat diet. Plasma potassium concentration also decreased modestly during the initial 2 weeks of the high-fat diet when plasma aldosterone concentration tended to increase, but during the remainder of the study, values were not significantly different from control. Plasma protein concentration increased during weeks 3 to 6 of the high-fat diet. There were no significant changes in either plasma sodium concentration or hematocrit throughout the entire 6 weeks of the high-fat diet.

**Discussion**

Dogs fed a high-fat diet for several weeks exhibit many of the hemodynamic, neurohormonal, renal, and metabolic changes associated with obesity in human subjects, including weight gain, sodium retention, hypertension, tachycardia, hyperinsulinemia, insulin resistance, and activation of the sympathetic and renin–angiotensin systems.2,11,28–33 The current findings demonstrate that PBA can completely abolish the sympathetic activation and hypertension and attenuate the tachycardia associated with obesity. In contrast to these impressive cardiovascular responses, PBA did not affect the hyperinsulinemia and hyperglycemia of obesity, indicating that the insulin resistance associated with weight gain may be independent of increased sympathetic activity.

There is considerable evidence for increased activation of the sympathetic nervous system throughout the evolution of obesity hypertension.1–12 We found that plasma NE concentration, an indirect measure of sympathetic activity, increased during the progression of obesity hypertension. Although statistically significant increments in plasma NE concentration have been reported in some experimental and clinical studies of obesity hypertension,7,28 this is not a consistent finding.5,30,34 This inability to consistently measure statistically significant increases in plasma NE, despite sympathetic activation, is perhaps not too surprising, because the increased blood volume and cardiac output associated with
obesity hypertension would be expected to lower circulating levels of NE by dilution and increased tissue extraction, respectively. Furthermore, this global index of sympathetic activation does not address differences in regional sympathetic outflow, which are differentially activated in obesity. Measurements demonstrating increased renal NE spillover in both the early prehypertensive and advanced hypertensive stages of obesity suggest that the renal nerves may provide the critical link between increased central sympathetic outflow and impaired renal excretory function that leads to and sustains obesity hypertension. This is strongly supported by an experimental study demonstrating that renal denervation completely abolishes the hypertension that is normally induced by feeding dogs a high-fat diet.

Because the renal nerves appear to play a critical role in mediating increases in arterial pressure in obesity, it was reasonable to hypothesize that PBA would lead to pronounced and sustained reductions in arterial pressure in dogs fed a high-fat diet. The rationale for this hypothesis was based on studies indicating that baroreflex activation has sustained effects to suppress renal sympathetic nerve activity and promote sodium excretion, responses expected to lead to long-term reductions in arterial pressure. Indeed, in the present study, PBA not only abolished the increase in plasma NE concentration and the hypertension induced by the high-fat diet, it even reduced MAP to below control levels. However, this impressive sustained fall in arterial pressure is not a universal response to PBA in all forms of hypertension. For example, the long-term blood pressure–lowering effects of PBA are markedly diminished in obesity hypertension, it was expected, given that renal sympathetic nerve activity is suppressed in Ang II hypertension as a result of the natural engagement of the baroreflex, but other considerations are also relevant as discussed below. In any case, it is clear from the current findings that PBA can completely counteract the increased sympathetic activation and attendant hypertension of obesity.

We did not evaluate the complete time course of the blood pressure–lowering effects of PBA before fat feeding, and, thus, we cannot state with certainty whether there is a differential arterial pressure response to PBA in obese compared with lean animals. The virtually identical reduction in MAP after 48 hours of baroreflex activation before and after fat feeding would suggest that the long-term blood pressure–lowering effects of PBA are not influenced by weight gain. Because the present study was conducted at approximately the same time and under similar conditions as our earlier study of Ang II hypertension, comparisons of baroreflex responses in obese dogs to the control responses in dogs before infusions of Ang II are reasonable and are illustrated in Figure 3. Given this caveat, it would appear from Figure 3 that the long-term blood pressure–lowering effects of the baroreflex are no greater in obese than in lean animals, despite higher arterial pressure and sympathetic activity in the former. This may reflect an inability of the baroreflex to suppress sympathetic activity to the same nadir in obese compared with lean dogs, presumably because of the sustained central sympathoexcitatory influences in obesity, which play a key role in the pathogenesis of the hypertension. In the present study, PBA did suppress the elevated circulating levels of NE in obesity to, but not below, control values, whereas in lean dogs, PBA consistently suppresses plasma NE concentration to levels considerably below normal (to \( \approx 60\% \) of control). Because sympathetic outflow is increased in obesity and contributes significantly to hypertension, we would have expected a greater fall in arterial pressure in obese compared with lean dogs if PBA reduced sympathetic activity to the same absolute level in both conditions. This contention is consistent with previous reports demonstrating a greater reduction in arterial pressure in obese hypertensive dogs and people compared with lean normotensive subjects during compete autonomic withdrawal by acute blockade of ganglionic transmission.

Maintenance of sodium balance at a reduced arterial pressure indicates that PBA has a sustained effect to enhance renal excretory function. In our previous studies, modest sodium retention occurred on day 1 of baroreflex activation (Figure 3). As we have discussed previously, the initial sodium retention on day 1 of baroreflex activation can be accounted for by the abrupt and pronounced fall in arterial pressure associated with the acute hemodynamic effects of baroreflex activation. An abrupt fall in MAP of \( \approx 20 \) mm Hg, a typical response to baroreflex activation in all
of our studies, would be expected to decrease sodium excretion unless sufficiently offset by a simultaneous increase in renal excretory function. Because sodium retention did not occur on day 1 of PBA in obese dogs, we presume that the acute effects of baroreflex activation to suppress renal sympathetic nerve activity and promote sodium excretion were more pronounced in obese dogs with higher prevailing levels of renal sympathetic nerve activity than in either normotensive or Ang II hypertensive dogs with normal or reduced renal sympathetic outflow, respectively. Furthermore, theoretical analyses indicate that the sympathetically mediated hemodynamic changes that account for the acute fall in arterial pressure during baroreflex activation would not be expected to result in a sustained lowering of arterial pressure without persistent increases in renal excretory function. Based on the observations that baroreflexes have sustained effects to suppress renal sympathetic nerve activity and promote sodium excretion, we speculate that the long-term blood pressure–lowering effects of PBA are mediated primarily by renal sympathoinhibition. Computer simulations in support of the above hypotheses have been published previously.

Activation of the renin–angiotensin system is postulated to be a mediator of obesity hypertension, and increased renal sympathetic nerve activity may be a chronic stimulus for renin secretion. Although increases in PRA have been reported in experimental animals and human subjects during the progression of obesity hypertension, this has not been a consistent finding even among different studies conducted from the same laboratories. The temporal changes in PRA and arterial pressure throughout the 6 weeks of the high-fat diet in the present study may provide insight into the variable measures of PRA in obesity. GFR is elevated in the initial stages of obesity, and, therefore, sodium retention must reflect increased tubular reabsorption. Because increased renal nerve activity promotes sodium reabsorption before the macula densa, this would be a stimulus for renin secretion during the early stages of weight gain, including the initial weeks of the high-fat diet in the present study. In turn, the generation of Ang II would also stimulate sodium reabsorption. As a result of salt and water retention and the concomitant, progressive increase in arterial pressure, sodium delivery to the macula densa would increase and tend to counterbalance the neurally mediated drive to increase renin secretion. Thus, under more chronic conditions, when body weight and arterial pressure are relatively stable, such as after 4 weeks of fat feeding in the present study, measurements of PRA would less likely reflect the sustained stimulatory effects of the renal nerves because of the opposing inhibitory effects of increased arterial pressure. In any case, despite the equivocal PRA values reported in obesity, studies in which Ang II receptor antagonists were chronically administered in canine and rodent models of diet-induced obesity indicate that the renin–angiotensin system plays a role in both the early evolution and the chronic maintenance of the hypertension.

Neurally modulated renin secretion also appears to be an important determinant of the long-term blood pressure response to baroreflex activation. Of particular significance, the marked fall in arterial pressure in response to PBA in the present study was not associated with activation of the renin–angiotensin system. The absence of an increase in PRA, despite the large fall in arterial pressure, suggests the presence of an inhibitory influence on renin secretion during PBA, presumably because of suppression of renal sympathetic nerve activity. Were it not for this renal sympathoinhibitory effect of the baroreflex to counteract pressure-dependent renin release, it is likely that the antinatriuretic effects of high circulating levels of Ang II would have diminished the long-term blood pressure–lowering effects of PBA in the present study. This contention is supported by the markedly diminished blood pressure–lowering effects of PBA in Ang II hypertension (Figure 3).

The tachycardia of obesity hypertension is associated with impaired baroreflex control of both sympathetic and vagal outflow. However, despite increases in sympathetic activity to the kidneys and the skeletal muscle vasculature, there is no clear increase in sympathetic outflow to the heart in obesity hypertension, clearly illustrating the regional differentiation of sympathetic responses. More specific to the present model of obesity hypertension, studies using autonomic blockade have demonstrated that the increased heart rate in dogs fed a high-fat diet is because of decreased vagal tone rather than increased sympathetic activity. Based on these findings, it is likely that the attenuation of the tachycardia during PBA in the present study was predominantly a vagally mediated response to baroreflex activation. This interpretation is consistent with a preliminary report indicating that chronic α- and β-adrenergic blockade, while markedly reducing arterial pressure, did not influence the elevated heart rate in dogs with established obesity hypertension. Finally, because the tachycardia in the current model of obesity hypertension is because of altered autonomic input, the incomplete normalization of heart rate by PBA, compared with the total abolition of hypertension, suggests a greater potential for baroreflex modulation of sympathetic rather than vagal activity in obesity hypertension. Nonetheless, the importance of vagally mediated responses to PBA in obesity should not be dismissed. By ameliorating the parasympathetic dysfunction of obesity hypertension, PBA may prevent and arrest life-threatening arrhythmias.

Insulin resistance is commonly associated with obesity, although the mechanisms responsible are unclear. One hypothesis is that insulin resistance is because of neurally mediated vasoconstriction in skeletal muscle, a major site of insulin resistance. According to this concept, by decreasing muscle blood flow, increased sympathetic activity would decrease delivery of insulin and glucose and impair glucose uptake in skeletal muscle. The evidence in support of this concept comes from acute studies after neurally induced vasoconstriction, and, therefore, the overall relevance of such transient events to the chronic hyperinsulinemia and hyperglycemia of obesity hypertension is unclear. Furthermore, despite increases in sympathetic outflow to several vascular beds, including the skeletal muscle vasculature, there is little evidence that basal blood flow is decreased in these tissues. In the present study, PBA-induced sympathoinhibition completely abolished the hypertension without affecting the hyperinsulinemia or hyperglycemia associated with obesity hypertension.
with weight gain. This adds to the data questioning the hypothesis that increased sympathetic activity, by any mechanism, contributes appreciably to the insulin resistance of obesity hypertension. The differential effect of PBA on arterial pressure and insulin resistance in the present study is consistent with the findings reported in dogs fed a high-fat diet while being chronically administered α- and β-adrenergic receptor antagonists. In this study, chronic adrenergic blockade prevented the normal induction of hypertension during the high-fat diet but did not attenuate either weight gain or the associated insulin resistance, as determined by the euglycemic hyperinsulinemic clamp method. Thus, unlike the hypertension, the insulin resistance of obesity hypertension appears to be independent of sympathetic activation. On the other hand, there is both experimental and clinical evidence that central inhibition of sympathetic outflow with agents that bind either α2- or imidazoline receptors does improve insulin resistance. Thus, the mechanisms that account for the differential effects of the central sympathetic, adrenergic receptors blocking agents, and baroreflex activation on insulin resistance are unclear at present. An alternate explanation of the potential linkage between the sympathetic nervous system and insulin resistance suggests that it is hyperinsulinemia that activates the sympathetic nervous system rather than increased sympathetic activity causing insulin resistance. Although a temporal relationship between increments in plasma levels of insulin and NE is apparent in the present study, multiple studies do not support a cause-and-effect relationship between hyperinsulinemia and activation of the sympathetic nervous system. The present study was not designed to test this important hypothesis. A potential limitation in the current experimental design was not having a time-control group of dogs that were not subjected to baroreflex activation, particularly as dietary fat was reduced during the week preceding PBA. However, we feel that this is not an important issue for several reasons. First, the current experimental design was based on a similar protocol in dogs in which the weight gain after 4 weeks of a high-fat diet was comparable to the increase in body weight in the present study. As in the present study, when dietary fat was reduced during week 5 in this earlier investigation, there was a little additional increase in body weight and no further changes in cardiovascular, neuroendocrine, renal, and metabolic responses from week 4 values. In addition, in the present study, the reduction in fat intake occurred ≥48 hours before PBA. Finally, after PBA, all of the measured responses returned to week 4 levels during the recovery period. Therefore, it is unlikely that any of the changes observed during week 5 of baroreflex activation were because of reduced fat intake rather than because of PBA.

Perspectives
Emerging evidence indicates that baroreflexes do not totally reset in hypertension and have sustained effects to suppress renal sympathetic nerve activity and promote sodium excretion, responses that lead to a fall in arterial pressure. In light of the striking sympathoinhibitory and antihypertensive effects of PBA in the present study and the observations that baroreflex activity is increased in obesity hypertension, it would appear that the baroreflex normally attenuates the sympathoexcitatory and hypertension of this most prevalent form of primary hypertension. Therefore, because acute determinations of baroreflex function indicate that baroreflex suppression of sympathetic activity is progressively impaired throughout the evolution of obesity hypertension, the recent studies indicating that baroreflexes play a role in the long-term regulation of arterial pressure support the notion that baroreflex dysfunction may make an important contribution to the sustained sympathetic activation and hypertension associated with obesity. Finally, because sympathetic activation is a common feature of primary hypertension and a sustained response (presumably reflexly mediated by unloading baroreceptors) to some forms of antihypertensive therapy, including diuretic treatment, the current technology for suppressing central sympathetic outflow by activating the carotid baroreflex may prove to be of valuable adjunct therapy in patients in whom blood pressure is difficult to control despite treatment with multiple medications. Indeed, clinical trials are now underway to evaluate the efficacy of this technology in lowering blood pressure in patients with severe refractory hypertension that is resistant to drug therapy.

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