Insulin Resistance, Hyperinsulinemia, and Hypertension: Causes, Consequences, or Merely Correlations? (43862B)

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Abstract. **Resistance to the metabolic effects of insulin and compensatory hyperinsulinemia have been postulated to mediate human essential hypertension, especially when associated with obesity. Evidence supporting this hypothesis has come mainly from epidemiological studies showing correlations between insulin resistance, hyperinsulinemia, and blood pressure, and from short-term studies suggesting that insulin has renal and sympathetic effects that could raise blood pressure if the effects were sustained. However, there have been no studies demonstrating a direct causal relationship between chronic hypertension and insulin resistance or hyperinsulinemia in humans. The few long-term studies that have been conducted in dogs and humans do not support the hypothesis that hyperinsulinemia causes hypertension or potentiates the hypertensive effects of other pressor agents such as angiotensin II or increased adrenergic tone. To the contrary, multiple studies in dogs and in humans suggest that the vasodilator action of insulin tends to reduce blood pressure. Although resistance to insulin's metabolic effects has been suggested to be essential for hyperinsulinemia to cause hypertension, chronic increases in plasma insulin concentrations do not cause hypertension in dogs or humans even in the presence of insulin resistance. Also, recent studies have also shown that the blood pressure-lowering effects of antihyperglycemic agents, initially believed to lower blood pressure by decreasing insulin resistance, may be unrelated to their effects on insulin sensitivity. Obesity appears to be a key factor in accounting for correlations between insulin resistance, hyperinsulinemia, and hypertension, but increased blood pressure in obesity does not appear to be mediated by insulin resistance and hyperinsulinemia. Although insulin resistance and hyperinsulinemia may not be directly linked to hypertension, there is increasing evidence that metabolic abnormalities associated with insulin resistance may increase the risk of cardiovascular disease (e.g., coronary artery disease) associated with hypertension and Type II diabetes. For this reason, further studies of the long-term effects of insulin resistance on cardiovascular, renal, and metabolic functions are needed.** [P.S.E.B.M. 1995, Vol 208]

In the past several years, there has been growing interest in the hypothesis that resistance to the metabolic effects of insulin resistance and compensatory hyperinsulinemia may contribute to increased blood pressure and essential hypertension, especially when associated with obesity (1–8). The observation that insulin resistance may be present in some lean hypertensive patients (5) has fueled speculation that these metabolic abnormalities may play a more pervasive role in hypertension than previously believed.

When we began our studies on mechanisms of obesity-induced hypertension, we were impressed with the many publications showing correlations among insulin resistance, hyperinsulinemia and blood pressure (1–7) and with results of acute studies demonstrating that insulin has multiple physiological effects that would tend to elevate blood pressure, if these effects were sustained or not overridden by other blood pressure stabilizing mechanisms (10–12).

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0037-9727/95/2084-0317$10.50/0

Based on the available evidence, we initially believed that hyperinsulinemia, occurring as a compensation for insulin resistance, was a likely candidate to link obesity with hypertension. Certainly, the evidence that insulin resistance and hyperinsulinemia are often associated with hypertension was compelling. However, a critical question that had not been answered at that time was whether chronic hyperinsulinemia could actually cause hypertension. Therefore, our first experiments in this area were aimed at determining whether chronic increases in plasma insulin, comparable to those found in obesity, could raise blood pressure. To our disappointment, we found in a number of studies that hyperinsulinemia, lasting for as long as 28 days, did not elevate blood pressure but instead tended to reduce it (13–16). These findings, along with recent observations that humans with chronic hyperinsulinemia due to insulinoma are not hypertensive (17, 18), led us to question the widely held view that hyperinsulinemia *per se* was a major factor in the etiology of hypertension (19–21). More recently, attention has turned to the possibility that insulin resistance, acting in conjunction with hyperinsulinemia or via mechanisms that are independent of hyperinsulinemia, may be a key link between obesity and hypertension. In this brief review, we consider this hypothesis and the experimental evidence for cause-and-effect relationships between hyperinsulinemia, insulin resistance, and hypertension.

Is Hyperinsulinemia or Insulin Resistance Correlated to Blood Pressure Independent of Obesity?

Broadly defined, insulin resistance refers to a subnormal response to a given concentration of insulin. However, this term is often used to describe an impairment of insulin's action on glucose homeostasis. Even with this restriction, the term, insulin resistance, can have several different meanings, depending on the methods of assessment and the type of abnormalities that cause impaired insulin action. For example, when insulin resistance is defined by fasting hyperinsulinemia, the most likely cause is decreased insulin-mediated suppression of hepatic glucose output (22). However, when insulin resistance is defined by methods that assess the ability of insulin to provide glucose disposal (e.g., acute glucose loading, euglycemic clamp), the most likely cause is decreased action of insulin on skeletal muscle glucose uptake (22). Presently, it is not clear which of these measures of insulin resistance (if any) best predicts cardiovascular diseases.

There have been several reports of positive correlations among blood pressure, the degree of insulin resistance (assessed by fasting hyperinsulinemia or glucose disposal following oral or intravenous glucose loads), and plasma insulin concentration (2, 3, 7, 11, 23). These associations are especially prominent in obese subjects, but some studies also suggest that insulin resistance may be present in lean hypertensive subjects. Ferrannini *et al.* (5, 6) reported that whole-body glucose uptake during a hyperinsulinemic-euglycemic clamp was reduced by 30%–40% in lean hypertensive patients compared with normotensive controls; also, the severity of hypertension in these patients correlated with the degree of insulin resistance. Several studies, however, have not found correlations between insulin and blood pressure (24–27). In a study of 100 obese hypertensive patients and 78 obese normotensive subjects, Grugni *et al.* (26) found no correlation between insulin and blood pressure. Asch *et al.* (27) reported that there were no significant differences in mean adjusted fasting insulin levels between normotensive and hypertensive subjects after stratification for obesity and glucose intolerance. Others have also found that the relationship between plasma insulin and blood pressure is very weak (28–30) or nonexistent (31).

Large scale epidemiological studies have also found a dissociation between hyperinsulinemia and hypertension (32, 33). Pima Indians and Mexican Americans often have insulin resistance and hyperinsulinemia, but rarely have hypertension (6, 24, 32). An inconsistent relationship has also been found between insulin and blood pressure in three different Pacific island populations (33). To the proponents of the insulin hypothesis, this lack of association between insulin and blood pressure in certain populations has suggested that a genetic predisposition toward insulin-mediated increases in blood pressure must be present before hypertension occurs. However, another interpretation is that there is no direct cause and effect relationship between insulin and hypertension. In other words, the reported correlations between insulin resistance, hyperinsulinemia, and hypertension may occur through parallel but unlinked mechanisms (Fig. 1). As discussed below, obesity appears to play an important role in accounting for correlations between insulin and blood pressure in many essential hypertensive subjects.

One explanation for the correlation between insulin and blood pressure that has recently been proposed is that hypertension causes insulin resistance and hyperinsulinemia via increased peripheral vascular resistance and decreased delivery of glucose and insulin to peripheral tissues, especially skeletal muscle (34, 35). We have recently analyzed this hypothesis quantitatively using a mathematical model of insulin and glucose homeostasis and found that large (50%) reductions in skeletal muscle blood flow, or the failure of skeletal muscles to vasodilate after ingestion of a large glucose load, can slightly impair the rapidity of glucose

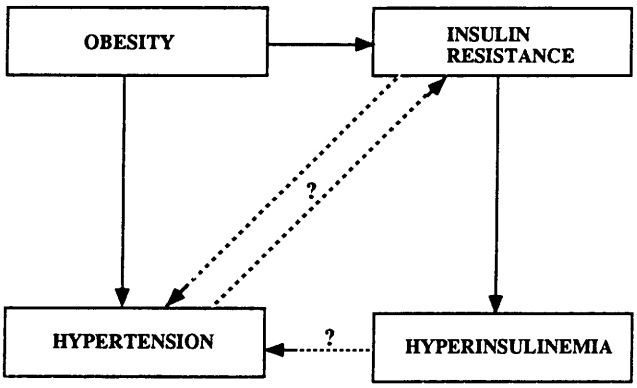

Figure 1. Postulated relationships between obesity, hyperinsulinemia, insulin resistance, and hypertension. Direct cause-and-effect relationships have been demonstrated between obesity and hypertension, and between obesity and insulin resistance. However, causal relationships between insulin resistance and hypertension, and between hyperinsulinemia and hypertension, have not been clearly established. Thus, correlations between insulin resistance, hyperinsulinemia, and hypertension could occur through parallel but unlinked mechanisms related to the effects of obesity on blood pressure and on insulin resistance.

disposal (22, 36); however, even large reductions in skeletal muscle blood flow did not cause fasting hyperinsulinemia as occurs in insulin resistant subjects (22). More important, there is very little evidence for decreased skeletal muscle blood flow in hypertensive, insulin resistant subjects (37, 38). Another key observation that makes it unlikely that insulin resistance occurs secondary to increased blood pressure is that several forms of hypertension, such as renovascular or mineralocorticoid hypertension, are not associated with insulin resistance (39–42). Also, arguing against the hypothesis that insulin resistance is secondary to increased blood pressure and altered peripheral blood flow is the fact that insulin resistance appears to be due mainly to postreceptor changes in intracellular signaling (43). It is difficult to envision a mechanism by which changes in tissue blood flow or hypertension *per se* could induce this type of abnormality. These and other observations provide little support for the hypothesis that insulin resistance and hyperinsulinemia occur primarily because of hemodynamic changes associated with hypertension.

One question that deserves further consideration is whether there actually is a good correlation between insulin and blood pressure, independent of obesity. Because obesity is an important cause of hypertension as well as insulin resistance, the relationship between increased blood pressure and insulin resistance may be due, in part, to increased body weight (Fig. 1). A recent study by Denker and Pollock (44) illustrates how obesity can confound the analysis of insulin resistance in hypertension. In this meta-analysis of several published studies, significant correlations between fasting serum insulin and systolic and diastolic blood pressures were found, leading to the conclusion that hyperinsulinemia might be important in the pathogenesis of essential hypertension. However, data in three of the studies used for this analysis (3, 7, 45) were obtained from obese hypertensive subjects; also, in another of the studies, the only relationship between insulin and blood pressure observed was dependent upon body mass index (33). Table I shows a reanalysis of the studies cited by Denker and Pollock, that employed lean hypertensive subjects (5, 25, 46, 47) along with four other studies of lean hypertensive and normotensive subjects (48–51). Overall, these studies suggest that fasting hyperinsulinemia may not be a characteristic of essential hypertension if the subjects are carefully matched for body mass index and other indices of obesity.

The fact that fasting insulin levels may not be markedly different in essential hypertensive and normotensive subjects, if body mass index is comparable, does not necessarily imply that transients of glucose disposal (as assessed by the euglycemic clamp method or by glucose tolerance tests) are the same in normotensive and hypertensive subjects. Only a few studies have directly assessed whether there are differences in glucose disposal in normotensive and hypertensive individuals who have been carefully matched for body mass index. Also, most of these studies have used large glucose loads, and it is not clear whether there are significant differences in insulin-glucose kinetics in hypertensive compared with normotensive subjects after eating a typical meal. Another question that has not been answered is whether transient abnormalities of glucose disposal following a glucose load are more or less predictive of cardiovascular disease compared with continuous hyperinsulinemia lasting throughout the day, including periods of fasting. Therefore, further study of whether essential hypertension is truly an insulin resistant state, independent of obesity, seems warranted. And, we should keep in mind that the presence or absence of a correlation between insulin and blood pressure does not prove or disprove the insulin hypothesis of hypertension. In

Table I. Plasma Insulin Concentration (uU/ml) and Body Mass Index (BMI, kg/m^2) in Non-Obese Essential Hypertensive and Normotensive Subjects

	Hypertensives			Normotensives		
	(n)	Insulin	BMI	(n)	Insulin	BMI
Ferrani	13	7	26	11	7	25
Mbanya	7	4.3	24.2	8	5.6	24.3
Sechi	17	8.1	24	14	5.7	23.2
Natali	8	12	27	7	10	26
Giugliano	30	20	25.8	28	19	26
Marigliano	7	13.8	23.1	21	10.7	22.4
Resnick	20	14	27.4	20	14	28.4
Lembo	14	6	25.2	12	5	25.4
Sum	116			121		
Average		10.7 ± 1.7	25.3 ± 0.5		9.6 ± 1.6	25.1 ± 0.6

many ways, emphasis on such correlations only serves to obscure the real issue of whether insulin resistance and hyperinsulinemia are involved in causing hypertension.

Does Hyperinsulinemia Cause Hypertension?

Acute Effects of Hyperinsulinemia on Renal and Cardiovascular Systems. Multiple acute studies suggest that hyperinsulinemia may have effects on the kidneys that could conceivably lead to high blood pressure, if they were sustained. For example, acute insulin infusion reduces sodium excretion by increasing tubular reabsorption (10, 52, 53). Theoretically, a sustained antinatriuretic effect would expand extracellular fluid volume and gradually raise blood pressure. However, as discussed below, several studies in our laboratory indicate that insulin's antinatriuretic effects on the kidney are not sustained and do not increase blood pressure (19–21).

A second mechanism by which insulin has been suggested to elevate blood pressure is by activating the sympathetic nervous system (11, 12, 54). High caloric intake, often associated with hyperinsulinemia, stimulates sympathetic activity as assessed by indirect methods such as tissue norepinephrine turnover or by plasma and urinary catecholamines (11, 12, 54). Studies in humans (55–58) indicate that short-term insulin infusion at rates that raise plasma concentrations to pathophysiologic levels, caused marked increases in sympathetic activity in skeletal muscle; however, despite increased sympathetic activity, forearm vascular resistance decreased and blood pressure did not change significantly during insulin infusion in humans (55). There have been no published studies, to our knowledge, that have examined the long-term effects of insulin on sympathetic activity in humans.

In opposition to its acute effects on the kidneys and sympathetic nervous system, insulin also has vasodilator effects that tend to lower blood pressure (16, 55, 59, 60, 61). The net effect of insulin on cardiovascular and renal function is therefore complex, depending upon the relative contributions of these multiple actions. However, almost all of the acute studies published thus far indicate that physiological or pathophysiological levels of insulin do not raise blood pressure. More important, studying the acute effects of hyperinsulinemia does not provide an adequate test of the insulin hypothesis because the results of short-term studies often cannot be extrapolated to an understanding of chronic hypertension. There are many instances in which various control systems have been found to play a major role in short-term blood pressure regulation, but have very little effect on the long-term level of blood pressure. A prime example is the carotid sinus baroreceptors, which are extremely important in stabilizing blood pressure during acute disturbances, such as upright posture, but which probably have very little role in long-term blood pressure regulation (62, 63).

Chronic Effects of Hyperinsulinemia on Blood Pressure Regulation. Although multiple acute studies have examined insulin's cardiovascular effects, there have been relatively few studies of the chronic effects of insulin on blood pressure regulation. To directly test whether hyperinsulinemia *per se* can cause hypertension, we examined whether insulin infusion for several days or weeks, at rates that raise intrarenal, systemic, or central nervous system plasma concentrations to pathophysiologic levels, caused sustained increases in blood pressure or changes in renal function (13, 14, 15, 16, 64, 65).

In one study, we infused insulin directly into the renal artery of conscious dogs at rates calculated to increase intrarenal, but not systemic, insulin concentrations to levels comparable to those found in obese hypertensive subjects (64). If the direct antinatriuretic effects of insulin can cause hypertension, as has been postulated, then raising intrarenal insulin levels should also increase blood pressure in the absence of altered systemic insulin concentrations. However, chronic intrarenal insulin infusion failed to significantly alter mean arterial pressure and caused only a transient, mild sodium retention (Fig. 2). These observations suggest that the direct renal actions of insulin are very modest and not capable of causing hypertension in dogs.

We also recently tested the hypothesis that insulin acts directly on the brain to elevate blood pressure and heart rate. In these studies, insulin was infused directly into the cerebral circulation of conscious dogs, with or without simultaneous glucose infusion, via the vertebral or carotid arteries at rates that raised central nervous system (CNS), but not systemic, plasma insulin concentrations to levels comparable to those found in obese subjects (65). In none of these experiments did we detect significant changes in heart rate or mean arterial pressure during vertebral or carotid artery insulin infusion for as long as four days (65). These results provide no evidence that insulin, at pathophysiologic concentrations, acts directly on the brain to elevate arterial pressure.

Although there have been previous reports that injection of insulin directly into the carotid artery raises arterial pressure, pharmacologic doses of insulin were used (66); therefore, it is doubtful that pathophysiologic insulin levels, comparable to those found in obesity, have major direct central effects on sympathetic activity in the dog. Our finding that systemic infusions of insulin caused significant increases in heart rate that were mediated, in part, through β-adrenergic mechanisms (67), suggests that the peripheral actions of insulin may lead to compensatory activation

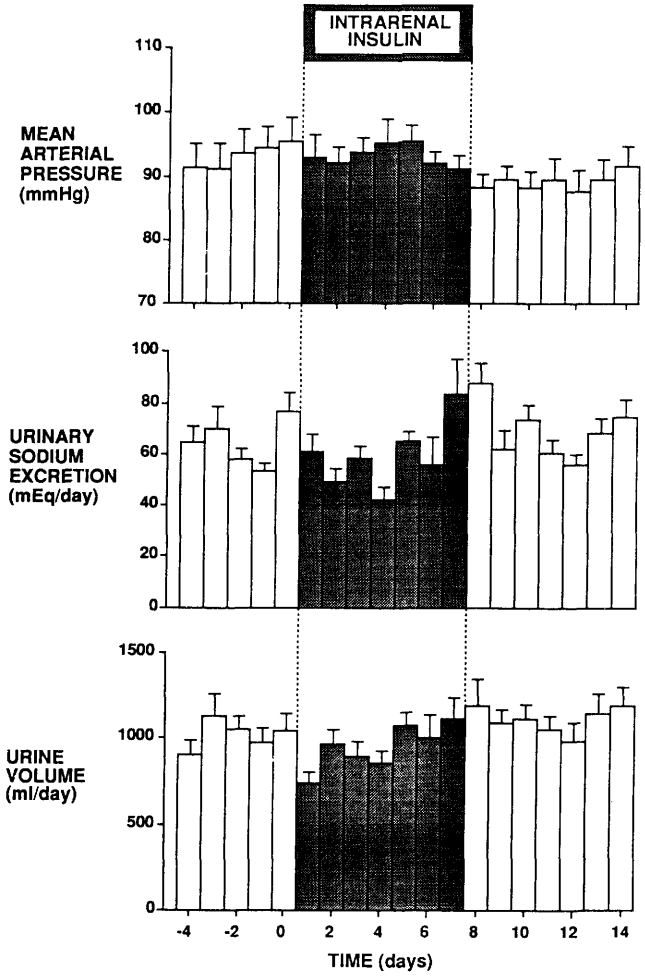

Figure 2. Effects of 7 days of intrarenal insulin infusion (1.0 mU/kg/min) on mean arterial pressure and urinary sodium excretion. These observations indicate that the direct renal actions of insulin on sodium excretion are modest and are not capable of causing hypertension in dogs. (Redrawn from data in Ref. 64.)

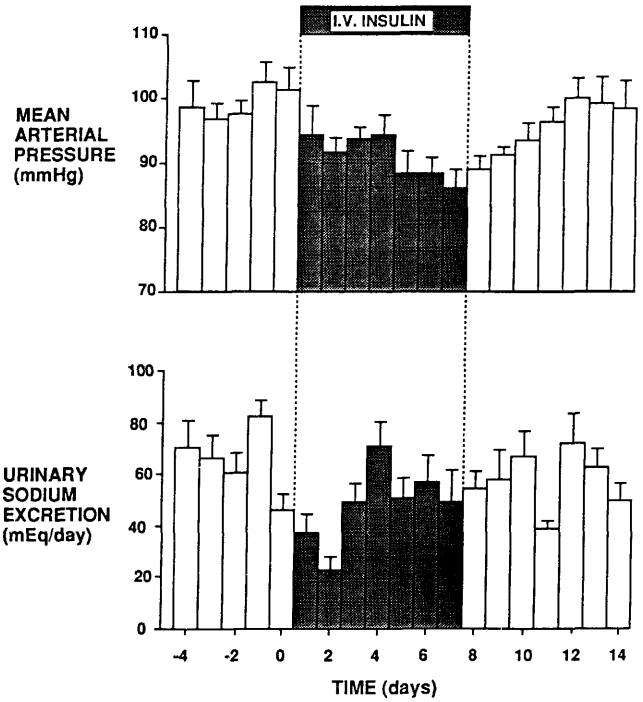

Figure 3. Effects of intravenous insulin infusion (1.0 mU/kg/min) for 7 days in normal dogs. These observations indicate that the combined systemic effects of insulin did not cause hypertension in normal dogs. (Redrawn from data in Ref. 14.)

of the sympathetic nervous system. For example, the peripheral vasodilator effect of insulin may activate reflex mechanisms that act to prevent reductions in blood pressure during systemic hyperinsulinemia. In patients with autonomic insufficiency and impaired baroreceptor function, insulin infusion causes marked reductions in blood pressure (68, 69). Thus, there is currently no direct evidence that the direct CNS actions of insulin are capable of causing sustained hypertension.

As a further test of the insulin hypothesis, we also determined whether the combined systemic actions of insulin, including effects on the sympathetic nervous system, the kidneys, and other possible cardiovascular effects, could cause hypertension (Fig. 3). In these studies, insulin was infused iv into normal conscious dogs at rates that raise plasma concentrations 5- to 6-fold while maintaining euglycemia (14). Although insulin infusion transiently reduced sodium excretion, sodium balance was reestablished in 2 to 3 days in the absence of increased blood pressure; in fact, blood pressure decreased by approximately 10 mm Hg during 7 days of hyperinsulinemia. Much of the sodium retention may have been secondary to the fall in blood pressure caused by peripheral vasodilation, rather than the direct effects of insulin on the kidney (14, 16, 64). Thus, in normal dogs, insulin is a potent peripheral vasodilator, has only a weak antinatriuretic effect, does not appear to chronically activate the sympathetic nervous system via direct effects on the CNS, and does not cause hypertension.

We also considered whether insulin might raise blood pressure when there was some preexisting impairment of kidney function, as occurs with other antinatriuretic hormones such as aldosterone. To test this possibility, we infused insulin for 28 days in dogs in which kidney mass was reduced by approximately 70% and sodium intake was maintained 4–5 times above normal (Fig. 4). Despite the propensity of these dogs toward developing hypertension, hyperinsulinemia decreased blood pressure by approximately 10 mm Hg during the first few days; after 28 days of insulin infusion, blood pressure was not significantly different from control, although insulin continued to maintain a hypotensive effect since blood pressure increased above control as soon as insulin infusion was stopped (15).

Although these studies provided no evidence that hyperinsulinemia *per se* causes hypertension, they did not rule out the possibility that insulin may potentiate the pressor effects of other stimuli, such as increased

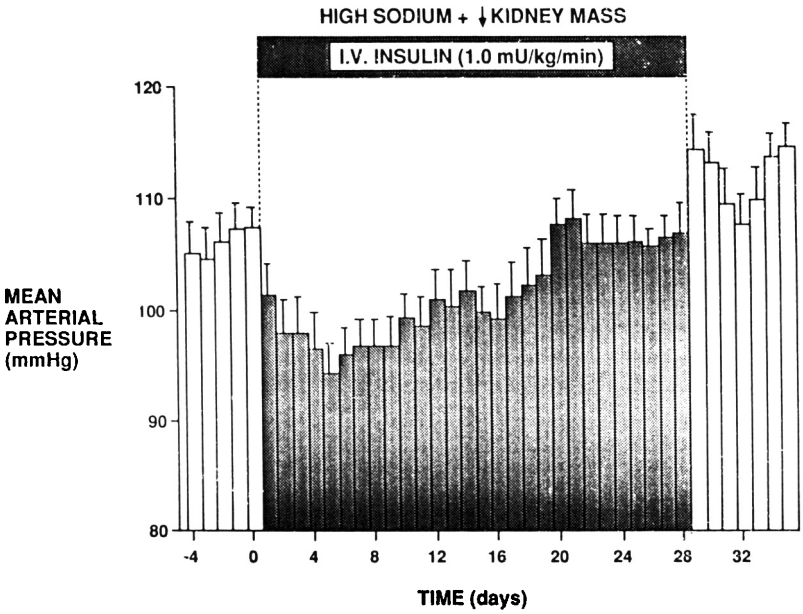

Figure 4. Effects of intravenous insulin infusion (1.0 mU/kg/min) for 28 days in dogs in which kidney mass was reduced by 70% and sodium intake was maintained at 4–5 times above normal. These findings indicate chronic hyperinsulinemia decreased, rather than increased, blood pressure. (Redrawn from data in Ref. 15.)

adrenergic activity or elevated angiotensin II (Ang II) levels. Some studies indicate that insulin resistant subjects, especially when they are obese, have increased activity of the renin-angiotensin and sympathetic systems (70). To test the hypothesis that insulin potentiates the blood pressure effects of Ang II, we infused insulin chronically in Ang II hypertensive dogs. Ang II was infused at a rate that produced mild hypertension for several days before insulin infusion was started. Subsequent infusion of insulin for 28 days, while Ang II infusion was kept constant, did not change mean arterial pressure further, indicating that insulin does not potentiate the chronic hypertensive effects of Ang II (15). In additional studies, we found no evidence that insulin exacerbates the chronic cardiovascular or renal effects of increased adrenergic tone (14). Thus, chronic hyperinsulinemia *per se* does not cause hypertension in dogs nor does it potentiate the blood pressure effects of other pressor stimuli such as Ang II or catecholamines. Taken together these observations provide strong evidence that hyperinsulinemia cannot account for hypertension associated with insulin resistance and obesity in dogs.

A question that must be considered, however, is whether the dog is an appropriate model for studying the chronic effects of hyperinsulinemia in humans. Although this question cannot be answered with certainty, there are several reasons to believe that the responses to insulin are very similar in humans and dogs. First, acute hyperinsulinemia causes virtually the same cardiovascular responses in dogs and humans—peripheral vasodilation, tachycardia, and little or no change in blood pressure as long as euglycemia is maintained and plasma insulin concentration is in the pathophysiologic range (14–16, 55, 59). Carefully controlled studies of the cardiovascular effects of chronic hyperinsulinemia in humans have not been conducted, but there are several reports that indicate that patients with very high levels of plasma insulin, due to insulinoma, do not have hypertension even in the presence of insulin resistance (17, 18, 71). Although it has been suggested that insulinoma patients may be resistant to the "hypertensinogenic" actions of insulin, there is no evidence to support this possibility. Overall, these observations suggest that the human cardiovascular responses to insulin are very similar to those of the dog and that hyperinsulinemia *per se* is not a sufficient stimulus for chronic hypertension in dogs or humans.

Chronic Hyperinsulinemia Causes Hypertension in Rats, in Contrast to Dogs and Humans. Although long-term studies in dogs, acute studies in humans, and studies in patients with insulinoma do not support the hypothesis that hyperinsulinemia is an important cause of hypertension, there are species variations in the blood pressure responses to insulin. Studies by Brands *et al.* (72, 73) in our laboratory have shown that hyperinsulinemia increases blood pressure, measured with intra-arterial catheters 24 hr a day using computerized methods, in rats. In one study of normal Sprague-Dawley rats, insulin infusion for 5 days at a rate that raised plasma concentration to pathophysiologic levels caused small but significant (8 mm Hg) increases in mean arterial pressure (72). In another study, we found that insulin-induced hypertension in rats was not salt sensitive; similar increases

in blood pressure were observed during 7 days of hyperinsulinemia in rats maintained on low, normal, or high sodium intakes (73). In contrast to obesity-induced hypertension, hyperinsulinemia in rats did not cause activation of the renin-angiotensin system (73). Thus, insulin elevated blood pressure in rats through mechanisms that are still unclear, but which may be very different from those that cause obesity hypertension.

Although some investigators have taken the observations in rats as support for a role of insulin in causing hypertension, it is still not clear whether the findings in rats are relevant to human hypertension. Hyperinsulinemia may activate pressor mechanisms in rats that are completely absent (or present at very low levels) in humans and dogs. Alternatively, dogs and humans may be protected from the hypertensive effects of insulin. The fact that insulin can elevate blood pressure in some species, such as the rat, is intriguing and keeps alive the possibility that there may be pathophysiologic conditions in which blood pressure regulatory systems are altered in a manner that allows insulin to express its hypertensive effects in humans and dogs. Further studies are needed to explore this possibility.

Is Insulin Resistance Required for Hyperinsulinemia to Cause Hypertension? Although hyperinsulinemia *per se* is not sufficient to raise blood pressure in dogs or humans, it has been hypothesized that the presence of insulin resistance may be a key element in allowing insulin to express its hypertensive action. For example, it has been suggested that the failure of chronic hyperinsulinemia to raise blood pressure in normal animals and humans may be due to offsetting effects of insulin's vasodilator action, which tends to lower blood pressure, and the hypertensive effects of insulin (e.g., effects on the kidneys and sympathetic nervous system), which tend to raise blood pressure. We showed that chronic hyperinsulinemia in normal dogs markedly reduced total peripheral resistance and increased cardiac output (16). Similarly, in normal humans hyperinsulinemia also decreases forearm vascular resistance and increases blood flow (55, 59). In contrast, the peripheral vasodilator actions of insulin are diminished or abolished in insulin-resistant subjects (58, 59, 61).

To determine if resistance to the vasodilator effects of insulin alters the long-term blood pressure responses to hyperinsulinemia, we studied the effects of chronic hyperinsulinemia in obese dogs that were resistant to the metabolic effects of insulin (74). Dogs were made obese by placing them on a high-fat diet and the presence of insulin resistance was confirmed by measurements of fasting hyperinsulinemia, by glucose tolerance tests, and by the euglycemia clamp method. Although chronic insulin infusion in these experiments failed to significantly decrease total peripheral resistance or raise cardiac output, indicating that the dogs were resistant to the vasodilator actions of insulin, there were no significant changes in mean arterial pressure (74). Thus, despite the presence of insulin resistance, insulin infusion failed to elevate blood pressure in obese dogs. Similarly, insulinoma patients are also insulin resistant but do not have increased blood pressure despite very high plasma insulin concentrations (18). Thus, the presence or absence of insulin resistance does not appear to greatly influence the chronic blood pressure responses to hyperinsulinemia in dogs or humans.

Can Long-Term Hyperinsulinemia Cause Hypertension by Stimulating Vascular Smooth Muscle Growth? Insulin has also been postulated to cause hypertension through a mitogenic effect on vascular smooth muscle (75). Previous studies suggest that high levels of insulin may stimulate proliferation of cultured vascular smooth muscle cells (76). More recent studies suggest that insulin, at concentrations of 1.7×10^{-10} to 1.7×10^{-6} *M*, has no significant effect on vascular smooth muscle cell DNA synthesis but may enhance the short-term effects of high levels of Ang II (10^{-7} *M*) on cell DNA synthesis (77, 78). Whether this effect has physiological relevance is unclear, because Ang II levels rarely exceed 10^{-10} *M*. However, the effect of insulin to enhance the mitogenic action of other growth factors was not sustained; during 14 weeks of insulin treatment, there was a gradual reduction in insulin's effect in enhancing Ang II mitogenicity in vascular smooth muscle (78). Thus, there is still doubt about whether insulin, even at very high concentrations, has long-term effects on vascular smooth muscle growth *in vitro*. Moreover, it is still not clear whether insulin, at concentrations similar to those found in obese hypertensives, can stimulate blood vessel growth *in vivo*. In one study often cited as evidence that insulin stimulates vascular growth *in vivo* (79), daily intra-arterial injections of insulin for 1–28 weeks in normal and diabetic dogs were reported to produce proliferative changes in the intima of the arterial wall, although quantitative analyses were not reported. However, extremely large doses of insulin (1000–3000 mU) were injected into the hindlimb as a bolus each day, making it difficult to extrapolate these results to a physiological or pathophysiological setting. Overall, there is little direct evidence that hyperinsulinemia, similar to that found in insulin-resistant subjects, is capable of causing significant stimulation of vascular smooth muscle growth *in vivo*.

There are other reasons that make it unlikely that stimulation of vascular smooth muscle growth by insulin plays a major role in causing chronic hypertension. As discussed below, theoretical and experimental studies indicate that increased peripheral vascular resistance is not a sufficient stimulus for chronic hy-

pertension unless increased resistance also occurs in the renal vasculature (62, 80). Although chronic hypertension is almost invariably associated with increased peripheral vascular resistance, such a change cannot cause chronic hypertension unless there is also a shift in the renal-pressure natriuresis mechanism (62, 80). A shift of pressure natriuresis could occur as a result of increased renal vascular resistance, due to vascular smooth muscle proliferation and decreased diameter of renal arteries and arterioles, but renal blood flow is not reduced in most obese, insulin resistant individuals. In fact, studies in experimental animals and humans indicate that renal blood flow is usually increased in obese, insulin-resistant subjects (81–83). Thus, even though the long-term effects of hyperinsulinemia on blood vessel growth have not been widely studied, there is currently no direct evidence that this is a major cause of hypertension.

Does Insulin Resistance Cause Hypertension Independent of Hyperinsulinemia?

Insulin resistance has been suggested to cause hypertension by raising total peripheral vascular resistance through mechanisms that are independent of hyperinsulinemia (84, 85). An interesting hypothesis is that insulin's vasodilator action normally helps to prevent hypertension initiated by other hypertensive stimuli and that decreased vascular sensitivity to insulin permits increased blood pressure in insulin resistant subjects (84). Insulin has been shown to stimulate sodium-potassium ATPase, which could inhibit vascular tone by hyperpolarizing vascular smooth muscle and increasing sodium-calcium exchange (84). Also, insulin may stimulate calcium ATPase activity which would tend to reduce intracellular calcium (84). And finally, insulin may also attenuate the contractile response of vascular smooth muscle to various constrictor agents (84). Presumably, if vascular smooth muscle were resistant to insulin's actions, these effects would be blunted and intracellular calcium would increase, causing vasoconstriction.

Although intracellular calcium concentration is elevated in vascular smooth muscle of some insulin resistant animals, such as the obese Zucker rat (84), the extent to which these changes are caused by insulin resistance, compared with other abnormalities, is still unclear. Currently, there is no direct evidence of a cause-and-effect relationship between insulin resistance and abnormalities of vascular smooth muscle transport that can lead to chronic hypertension. An observation that argues against this hypothesis is the fact that cardiac output is elevated and blood flow to many tissues is increased, rather than reduced, in obese, insulin-resistant humans and dogs (81, 86, 87). Experimental models of hypertension caused by excessive vasoconstriction are usually characterized by normal or reduced cardiac output and low tissue blood flows (62, 63). Conceptually, it seems unlikely that decreased action of a hormone that is primarily responsible for glucose regulation and that remains at relatively low concentrations except after meals, would be capable of disrupting the multiple mechanisms that operate to maintain normal blood pressure.

There are other considerations that argue even more strongly against excessive peripheral vasoconstriction as a primary cause of hypertension. Although increased peripheral vascular resistance is a hallmark of most forms of established hypertension, theoretical and experimental studies indicate that peripheral vasoconstriction cannot cause hypertension unless the constriction also occurs in renal vessels and shifts pressure natriuresis to higher blood pressures (62, 63, 80). In the absence of a resetting of pressure natriuresis, a rise in blood pressure solely due to increased peripheral vascular resistance would increase sodium excretion and decrease extracellular fluid volume until blood pressure eventually returned to normal (80, 88). This concept is illustrated in Figure 5, which shows the effects of increased peripheral vascular resistance without a shift of pressure natriuresis, on long-term blood pressure. Initially, a rise in peripheral resistance would rapidly increase blood pressure. At the same time, however, the hypertension would also cause a marked rise in sodium excretion, via pressure natriuresis. Eventually, the increased renal fluid output would decrease extracellular fluid volume and return blood pressure toward normal. In the absence of a resetting of pressure natriuresis, the only point at which sodium balance can be maintained is at the normal blood pressure.

Thus, increased peripheral vascular resistance, caused by decreased vasodilator effects of insulin on peripheral blood vessels, cannot cause chronic hypertension in the absence of a resetting of renal-pressure natriuresis. The rise in peripheral vascular resistance found in almost all forms of hypertension may be the result of autoregulatory adjustments that maintain normal tissue flow in the face of increased perfusion pressure, rather than a primary cause of hypertension (62, 63). On the other hand, if insulin resistance could, in some way, cause renal vasoconstriction and shift pressure natriuresis to higher levels, this could lead to hypertension. As discussed above, however, insulin resistance in patients with obesity is not associated with renal vasoconstriction. Marked decreases in renal vascular resistance and increased renal blood flow and GFR have been found in obese, insulin-resistant dogs (81, 82). Also, renal blood flow is increased in obese, insulin-resistant humans (83). These observations suggest that increased vascular resistance in peripheral

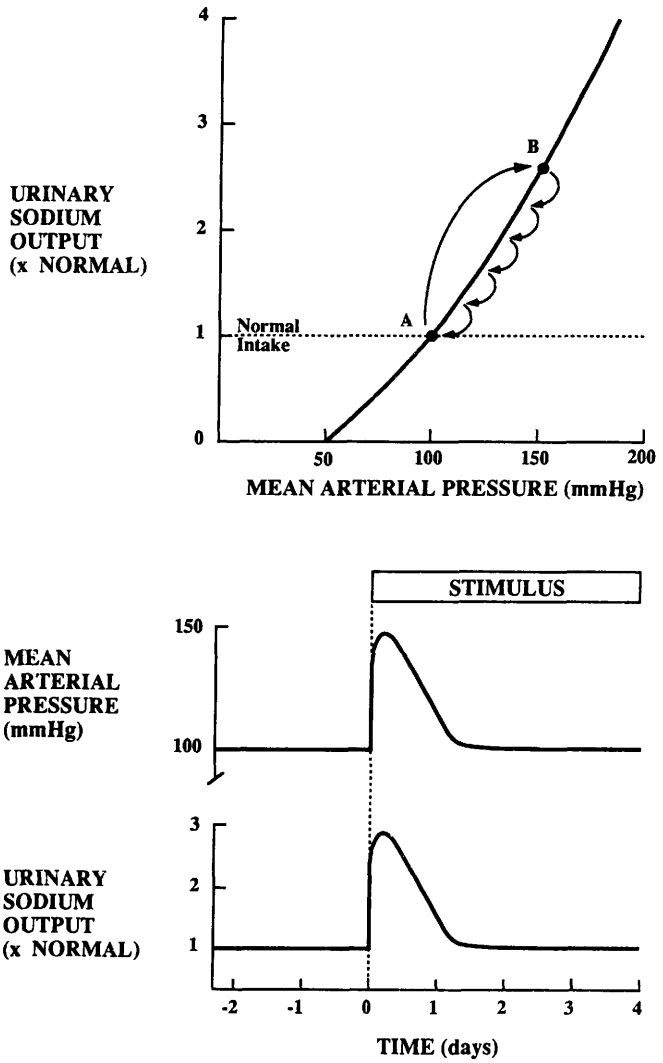

Figure 5. Predicted effects of increased peripheral resistance, without a change in the basic pressure-natriuresis relationship, on mean arterial pressure. Initially, increased peripheral vascular resistance raises blood pressure from Point A to Point B. However, increased blood pressure also elevates urinary sodium excretion, via pressure natriuresis. As long as sodium excretion exceeds sodium intake, extracellular fluid volume will decrease until blood pressure returns to the normal level (Point A). Point A is the only point at which balance between sodium intake and output can be achieved without a shift of pressure-natriuresis. Thus, peripheral vasoconstriction alone is not a sufficient stimulus for chronic hypertension. (Adapted with permission from Ref. 80.)

arterioles and/or the kidneys, due to a reduced vasodilator action of insulin secondary to insulin resistance, is probably not an important cause of hypertension.

Does Reducing Endogenous Insulin Secretion or Increasing Insulin Sensitivity Lower Blood Pressure in Insulin-Resistant Subjects?

Another approach used to test the insulin resistance/hyperinsulinemia concept of hypertension has been to reduce endogenous insulin secretion with somatostatin or to increase insulin sensitivity with antihyperglycemic agents. Somatostatin or analogs of somatostatin inhibit insulin secretion, but they do not eliminate insulin resistance, thereby providing a means of testing the contribution of hyperinsulinemia *per se* to increased blood pressure. Carretta *et al.* (89) found that somatostatin infusion reduced blood pressure by approximately 14 mm Hg in obese, hyperinsulinemic, hypertensive patients, but had little effect in normotensive subjects. Similarly, Reaven, *et al.* (90) reported that somatostatin prevented the development of fructose-induced hypertension in rats. It should be noted, however, that we have found no evidence that chronic fructose feeding causes hypertension in rats when mean arterial pressure was monitored continuously, 24 hr a day (91). Moreover, we have not been able to find any significant long-term effect of inhibition of insulin secretion on blood pressure in obese, insulin-resistant dogs or in obese Zucker rats (unpublished observations). However, even if somatostatin lowers blood pressure in insulin-resistant subjects (and there is some question about whether this assumption is correct), it does not necessarily follow that the effects of somatostatin on blood pressure are due to suppression of insulin secretion. Somatostatin has multiple actions on other hormone systems in addition to effects on metabolic functions that are independent of insulin and that may influence blood pressure regulation. To date, there have been no long-term studies that have clearly demonstrated that the acute or chronic blood pressure-lowering effects of somatostatin can be reversed by restoration of plasma insulin concentration. In one acute study, by Anderson and Marks' group in Iowa (92), somatostatin infusion for 2 hr in obese, insulin-resistant, hypertensive humans reduced forearm vascular resistance but lowered arterial pressure by only 3 mm Hg, despite causing marked suppression of plasma insulin concentration to levels far below those seen in normotensive insulin-sensitive individuals. In a review of this work, Anderson and Mark (59) noted that these small effects of somatostatin on blood pressure did not exceed those observed during time/vehicle control experiments. Thus, there is currently no direct evidence that the acute or chronic effects of somatostatin on blood pressure can be attributed to reduced plasma insulin levels.

Administration of antihyperglycemic agents that increase peripheral insulin sensitivity has also been used to test the hypothesis that insulin resistance contributes to hypertension. Landin *et al.* (93), in an uncontrolled study, reported that short-term administration of metformin, a biguanide antihyperglycemic drug, caused a significant reduction in blood pressure in a small group of insulin resistant, hypertensive men. However, as noted by Passa (94), metformin has been

used extensively in treating non-insulin-dependent diabetics in France for nearly 40 years, and there have been no reports that this drug modifies blood pressure in insulin-resistant, normotensive or hypertensive patients.

Several reports in rats, however, indicate that antihyperglycemic agents may increase insulin sensitivity and lower blood pressure. For example, the thiazolidenedione compound, pioglitazone, has been reported to reduce arterial pressure in Dahl salt-sensitive rats, which are somewhat insulin resistant compared with Dahl salt-resistant rats, but to have no effect on blood pressure in control rats (95). In obese, insulin-resistant Zucker rats, ciglitazone lowers arterial pressure while improving insulin sensitivity (96). Also, Fujiwara *et al.* (97) have reported that CS-045, another insulin-sensitizing thiazolidenedione agent, reduces blood pressure in obese Zucker rats while improving renal sodium excretion. Thus, several studies in insulin resistant rats suggest that antihyperglycemic agents that improve insulin sensitivity may also lower arterial pressure.

Although these observations are consistent with the hypothesis that insulin resistance contributes to hypertension in these models, they do not prove cause-and-effect relationships because the mechanisms by which these drugs lower blood pressure have not been clearly established. Dubey *et al.* (95) found that pioglitazone reduced arterial pressure in renal hypertensive rats, which are not insulin resistant or hyperinsulinemic, suggesting that the antihypertensive effect of these agents may be independent of changes in insulin sensitivity. The thiazolidenediones may inhibit calcium channels, which may account for their blood pressure-lowering actions independently of increased insulin sensitivity (96). Regardless of the exact mechanisms by which these antihyperglycemic agents lower blood pressure, there is no direct evidence that their blood pressure effects are due to improved insulin sensitivity.

Perspectives

Although insulin resistance and hyperinsulinemia have been postulated to play a key role in human essential hypertension, especially when associated with obesity, most of the available evidence for this hypothesis comes from correlations or from acute studies on the cardiovascular and renal actions of insulin. Correlations do not prove cause-and-effect relationships, and emphasis on such correlations has obscured the issue of whether insulin resistance and hyperinsulinemia actually cause hypertension. Acute studies suggest that insulin may have effects on the sympathetic nervous system and kidneys that could theoretically cause hypertension if they were sustained. However, studying the acute effects of hyperinsulinemia does not provide an adequate test of the insulin hypothesis because the results cannot be extrapolated to understand the mechanisms of a chronic disease such as hypertension. Chronic studies in dogs and humans clearly indicate that hyperinsulinemia *per se* is not sufficient to cause hypertension, even in the presence of insulin resistance. The fact that hyperinsulinemia raises blood pressure in some species, such as in the rat, raises the intriguing possibility that there may be pathophysiologic conditions in which blood pressure regulatory systems are altered in a way that unmasks a hypertensive action of insulin. Further studies are needed to explore this possibility, but at present there is little evidence that hyperinsulinemia contributes to hypertension in humans. The question of whether insulin resistance increases blood pressure, independent of hyperinsulinemia, has not been completely answered with experimental studies. Although several studies have shown that improvement of insulin sensitivity with antihyperglycemic agents also lowers blood pressure in rats, and possibly in humans, there is no convincing evidence that the antihypertensive effect of these drugs is linked to enhanced insulin sensitivity.

The fact that there is no direct proof for a causal relationship between insulin resistance, hyperinsulinemia, and hypertension does not necessarily imply that such a relationship cannot exist. Unfortunately, many investigators and clinicians have assumed that correlations among these variables signify cause-and-effect relationships and have devised therapeutic strategies based on an unproven hypothesis. More caution should be exercised in view of the large amount of evidence that is not consistent with the insulin hypothesis of hypertension.

Even though insulin resistance and compensatory hyperinsulinemia have not been linked to hypertension, there is increasing evidence that metabolic abnormalities caused by insulin resistance may increase the risk of cardiovascular disease associated with hypertension and Type II diabetes. For this reason, further studies of the long-term effects of insulin resistance and hyperinsulinemia on cardiovascular, renal, and metabolic functions are needed. However, we should not let the flurry of speculation and interest in this area detract from studies of other mechanisms, especially those associate with obesity, that can alter renal function and raise blood pressure in essential hypertension.

The author's research was supported by National Institutes of Health Grant HL 39399, HL 23502, and HL 51971.

The authors thank Mrs. Ivadelle Osberg Heidke for excellent secretarial assistance.

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