Is High Blood Pressure a Late Manifestation of the Hypertension Syndrome?

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Because hypertension has generally been defined as a disease of elevated systolic and diastolic blood pressure, the goals of treating hypertension have been simply to normalize the blood pressure. It was believed that if normal blood pressure were achieved, patients with hypertension would experience significant reductions in the incidence of associated cardiovascular events. However, studies to assess cardiovascular events in patients with hypertension have repeatedly demonstrated that reducing blood pressure results in very impressive reductions in cerebrovascular disease but in reductions of only about 16% in coronary artery disease, which is far lower than what was statistically predicted from the reductions in blood pressure. Although there are probably several reasons for the poor rate of reductions in the incidence of coronary artery disease, one of the most compelling appears to be the realization that hypertension is not simply a disease of numbers but rather a complex inherited syndrome of cardiovascular risk factors, all of which contribute to the development of heart disease in these patients. Included in the hypertension syndrome are abnormalities of lipid profile and insulin resistance, changes in renal function, endocrine changes, obesity, abnormalities of coagulation factors, and changes in the structure and function of the left ventricle and of vascular smooth muscle in the vasculature. In many patients, high blood pressure is a late manifestation of this disease process and is preceded by some or all of the associated cardiovascular risk factors. This paradigm suggests that therapeutic strategies for hypertension should be interventions that target both the hemodynamic and nonhemodynamic mechanisms of this syndrome to more completely reduce cardiovascular morbidity and mortality in patients with hypertension. Am J Hypertens 1999; 12:215S–223S © 1999 American Journal of Hypertension, Ltd.

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Much of the focus in the management of hypertension has centered on reducing blood pressure to the normotensive range in the hope that this will decrease the cardiovascular morbidity and mortality so commonly associated with high blood pressure. Although there is no doubt that reduction of high blood pressure is important, particularly with respect to stroke, it has not resulted in the predicted decrease in coronary artery disease in patients treated for hypertension.1,2 One possible reason for this disappointing decrease in heart disease is that high blood pressure is a very late...
manifestation of a much broader syndrome of cardiovascular risk factors. These associated risk factors may be present for years before the onset of high blood pressure and may precipitate a coronary event either before or very soon after the onset of high blood pressure. In these patients, treatment of the high blood pressure will have very little impact on the outcome. In addition, it appears that many of the changes in vascular structure and function occur before the onset of high blood pressure and may be responsible for its ultimate development.

The development of high blood pressure in patients with hypertension may represent an advanced or perhaps irreversible stage of the disease process, and it is possible that treatment after this stage can only control blood pressure and slow the progression to cardiovascular disease. Identification and treatment of these patients before the onset of high blood pressure may provide a better opportunity for reversing the disease process and protecting patients from developing cardiovascular disease.

**COMPONENTS OF THE HYPERTENSION SYNDROME**

**Lipid Factors** Hypertension and lipid abnormalities often coexist. Each is an independent risk factor for cardiovascular events. Moreover, the likelihood of coronary events appears to be compounded when the two occur together. The explanation for this phenomenon is not clear. However, studies in modules of rats with genetic hypertension indicate that the vascular smooth muscle of the animals binds with a greater affinity to low-density lipoprotein than do the cells of normotensive control animals.

The presence of high blood pressure and hyperlipidemia is so common in patients with hypertension that many have argued that the high blood pressure itself may play a role in altering lipid metabolism, resulting in lipid abnormalities. However, recent data have demonstrated that high blood pressure and hyperlipidemia are genetically inherited and probably genetically linked, but are separate variables that frequently may present independently of one another. In a study comparing age-, gender-, and body-mass-index-matched patients with normotension with and without a family history of hypertension, the patients with a family history (hypertensive-prone patients) had significantly greater total cholesterol concentrations than did those without a family history of hypertension. This would suggest that lipid abnormalities in patients with a family history of hypertension precede blood pressure abnormalities in patients likely to develop high blood pressure over the next few years. Thus, these patients have two important cardiovascular risk factors, both of which appear to be inherited, occur independently of one another, and contribute to the development of heart disease. This may have important therapeutic implications, as studies using the occurrence of coronary events to judge the success of treatment of patients with hypertension have shown that the treatment of hypertension alone or of hypercholesterolemia alone produced modest results; only when both conditions were controlled was there a marked reduction in coronary artery disease.

**Left Ventricular Hypertrophy** Left ventricular hypertrophy frequently is considered an adaptive response to hypertension. Although blood pressure is treated aggressively in most patients with hypertension, left ventricular hypertrophy is ignored or is assumed to regress with the reduction of blood pressure. There is, however, a strong relationship between left ventricular muscle mass and the occurrence of cardiovascular events. Recent reports from the Framingham Heart Study have confirmed that echocardiographically measured left ventricular hypertrophy, independent of other risk factors, is clearly associated with a risk of cardiovascular events or death. Moreover, among people with hypertension, left ventricular hypertrophy appears to be an important predictor of patients destined to have pure cardiovascular outcomes.

Echocardiographic M-mode techniques make it possible to measure left ventricular wall thickness and chamber size, thus enabling accurate calculation of left ventricular muscle mass. Because of the sensitivity of the echocardiographic measurements, the prevalence of left ventricular hypertrophy in patients with hypertension is now known to be far greater than previously supposed. In a survey of an unselected clinic population of patients with hypertension, electrocardiography and chest radiography estimated a prevalence of left ventricular hypertrophy in the range of 5% to 10%, and echocardiography in the same patients indicated that almost 50% had an increased left ventricular muscle mass. Although sustained high blood pressure can produce secondary hypertrophy of the left ventricle, there is good evidence that left ventricular hypertrophy may actually precede the onset of hypertension or develop early in its course. A study of young persons (age < 30 years) with mild hypertension found that approximately 50% of these patients had higher measurements for septal and posterior wall thickness than the highest measurement found in an age-matched control group. Interestingly, subsequent blood pressure measurements indicated that many of these young patients with hypertension had normal or borderline blood pressure values; however, their echocardiographic measurements of wall thickness did not differ from the increased measurements obtained in
patients whose blood pressure was in the hypertensive range.

In a separate study, echocardiographic findings in normotensive children of normotensive parents were compared with those of age-, gender-, and body-mass-index-matched normotensive children of hypertensive parents. The offspring of the parents with hypertension had significantly greater left ventricular wall thickness and muscle mass than did the offspring of normotensive parents. Thus, in patients prone to hypertension, abnormalities of left ventricular muscle mass may occur before the development of high blood pressure. Therefore, left ventricular hypertrophy is another cardiovascular risk factor that appears to be genetically determined and commonly associated with high blood pressure, but its presence is independent of, and may occur before the onset of, high blood pressure.

Ventricular and Arterial Compliance Hypertension is characterized by structural changes in the cardiovascular system. Hypertrophy and hyperplasia of arterial and ventricular walls in association with increased deposit of connective tissue elements are common findings in patients with hypertension. These changes lead to stiffening of the walls, resulting in reduced arterial and ventricular compliance (diastolic dysfunction). Comparisons of patients with normotension and hypertension have established that cardiovascular compliance is not necessarily linked to an increase in blood pressure. Moreover, studies have suggested that abnormalities of compliance can precede the abnormalities of blood pressure and that they may not worsen with increasing blood pressure. A recent study comparing arterial function in normotensive subjects of hypertensive parents with that in normotensive subjects of normotensive parents showed that the patients with a family history of hypertension (hypertensive-prone patients) had abnormalities of arterial function despite the fact that they were normotensive. Similarly, in a study using an invasive technique to measure arterial compliance, normotensive subjects of hypertensive parents demonstrated a significant reduction in arterial compliance (stiffening) compared with normotensive subjects of normotensive parents. These findings suggest that the abnormalities of arterial structure and function frequently associated with hypertension may precede the onset of high blood pressure.

A similar patient model was used to assess ventricular compliance in hypertensive-prone patients. Transmitral flow characteristics, measured by Doppler echocardiography, have been used as an index of left ventricular filling during diastole; an increased ratio of late to early left ventricular filling reflects reduced compliance of the left ventricular wall. In patients with advanced stages of hypertension, this may result in congestive cardiac failure. It appears likely that the changes in ventricular compliance in patients with hypertension also precede the onset of high blood pressure. In a group of normotensive male college students matched for age, blood pressure, and left ventricular mass, those with a family history of hypertension had delayed diastolic filling compared with those who did not have a family history of hypertension.

Thus, the changes in compliance frequently associated with hypertension appear to precede the onset of high blood pressure and occur independently of the changes in blood pressure. Furthermore, it has been demonstrated that reduced compliance causes an increase in blood pressure and therefore may play a role in the pathophysiology of increased blood pressure.

Glucose and Insulin Metabolism In recent years, there has been growing interest in the presence of insulin resistance (syndrome X) in patients with hypertension. Multiple clinical studies have demonstrated an increased relative risk of cardiovascular events in patients resistant to insulin. Clinicians have long been aware that diabetes mellitus and hypertension often coexist. There is growing evidence that many patients with hypertension can be characterized as having borderline glucose intolerance and insulin resistance. These patients usually have normal fasting blood glucose concentrations and are not considered to have clinical diabetes. A large-scale population survey has indicated that approximately 50% of untreated patients with hypertension have glucose intolerance according to plasma glucose levels measured 2 h after a glucose load. This prevalence is far higher than that in normotensive controls. The explanation appears to be resistance to the action of insulin. In a recent study of well-matched groups of volunteers with normotension and patients with hypertension given a standard oral glucose tolerance test, glucose levels were found to be slightly higher in the group with hypertension than in the normotensive subjects. More impressively, during much of the 3-h study, plasma insulin concentrations were significantly higher in patients with hypertension than in their normotensive counterparts. The data also demonstrate that the problem is exaggerated by thiazide treatment, especially when β-blockers are added.

These findings are potentially important in explaining the high incidence of atherosclerotic disease in patients with hypertension. Insulin is a powerful growth factor that directly stimulates smooth muscle proliferation in the circulation. In addition, it plays an important role in promoting the action of other growth factors on vascular tissue. Moreover, insulin appears to enhance formation of atherosclerotic...
plaque by facilitating the transport of atherogenic lipid particles into the media of the vessel wall. In a recent comparison of patients with increased and normal plasma insulin levels, those with higher insulin levels had increased concentrations of triglycerides and total cholesterol but decreased levels of high-density lipoprotein. Increased insulin levels also appear to be associated with higher blood pressure. Several actions of insulin may result in increased blood pressure. It stimulates the sympathetic nervous system, probably through glucose-mediated effects on the hypothalamus. It also causes reabsorption of sodium by the kidney. These observations provide a possible explanation for the association of non-insulin-dependent diabetes with hypertension. Other reported effects of hyperinsulinemia include an increase in the pressor action of angiotensin II and angiotensin II-stimulated production of aldosterone. In one study, chronic administration of insulin to rats increased the blood pressure, which remained increased for several days after the insulin was discontinued.

It appears that insulin resistance and elevated insulin levels precede the increases in blood pressure. In a study comparing age-, gender-, and body-mass-index-matched patients with normotension with and without a family history of hypertension, insulin levels were significantly higher in the patients with a family history of hypertension than in those without. Furthermore, the insulin-to-glucose ratio, which correlates well with insulin resistance measured by the euglycemic clamp technique, demonstrated that patients with a family history of hypertension were less sensitive to their own insulin than were those without a family history, despite the presence of normal blood pressure. Similar findings were reported in a study of young black men: fasting plasma insulin concentrations were significantly greater in patients with borderline hypertension than in normal controls, and the young patients with hypertension exhibited a diminished capacity to clear glucose from their plasma. A similar picture of impaired glucose tolerance and compensatory hyperinsulinemia has been observed in normal offspring of patients with type 2 diabetes, suggesting a possible link between the mechanisms that mediate increased blood pressure and diabetes.

There is good evidence that insulin resistance and hyperinsulinemia are important cardiovascular risk factors. Early evidence linking diabetes and atherosclerosis came from the International Atherosclerosis Project. Later, in prospective population studies, increased insulin concentrations were implicated in the development of coronary artery disease. These studies have also shown that hyperinsulinemia is associated with increased levels of triglycerides and decreased concentrations of high-density lipoprotein cholesterol. Other studies have shown that changes in lipoprotein composition characteristic of non-insulin-dependent diabetes mellitus are extremely atherogenic. In the Paris Prospective Study, plasma insulin concentrations were a potent independent predictor of coronary artery disease. A prospective study of 982 men, the Helsinki Policemen Study, showed that high levels of plasma insulin were predictive of coronary artery disease, death, or nonfatal myocardial infarction over a 9.5-year follow-up. In the Prospective Cardiovascular Münster (PROCAM) study, hypertension, non-insulin-dependent diabetes mellitus, and hyperlipidemia were shown to be independent risk factors for coronary artery disease.

Renal Changes With recent interest in milder forms of hypertension, early changes in renal function have been observed. Differences in renal functional reserve have been demonstrated in children of parents with normotension compared with children of parents with hypertension. Thus, despite apparently normal renal function, the children of parents with hypertension appeared to be less able than the children of parents with normotension to increase their creatinine clearance in response to protein load and also were more likely to exhibit microalbuminuria. These data were confirmed in a later study that demonstrated significantly greater microalbuminuria in normotensive adults with a family history of hypertension than in matched normotensive adults without a family history of hypertension.

These data suggest that early changes in renal function may precede the development of and occur independently of high blood pressure. Moreover, the reduction in renal function may play a role in causing high blood pressure.

Obesity A large study demonstrated that patients with hypertension had a greater body mass index than well-matched male and female subjects with normotension in every age group. Obesity is associated with metabolic complications considered to be risk factors for cardiovascular disease, including insulin resistance, hyperinsulinemia, glucose intolerance, non-insulin-dependent diabetes mellitus, hypertension, and changes in concentration of plasma lipids and lipoproteins. Only recently has truncal obesity, characterized by a large waist-to-hip ratio (apple-shaped obesity), been shown to predict the risk of coronary artery disease. The mechanisms that link obesity with hypertension-lipid abnormalities are not clear. In view of the efficacy of weight loss and exercise in reducing blood pressure, it has been speculated that insulin provides the link between obesity and increased sympathetic nervous system activities.

The hyperglycemic clamp technique has been used to compare obese patients with hypertension with obese patients with normotension and lean controls to de-
termine whether additional hyperinsulinemia and insulin resistance are associated with obesity when hypertension is also present. The two obese groups were similar and showed greater insulin concentrations and insulin resistance than did their lean controls, but obesity and hypertension were not additive in these effects. When obese and nonobese patients with non-insulin-dependent diabetes mellitus with and without hypertension were compared, greater insulin resistance and hypertension were present in lean individuals with non-insulin-dependent diabetes but not in their obese counterparts.

Endocrine Changes The sympathetic nervous system and the renin-angiotensin system are believed to play an important role in the pathogenesis of high blood pressure. Many of the modern antihypertensive drugs work by interrupting these systems in order to reduce blood pressure. Recent studies have demonstrated that plasma norepinephrine levels and plasma renin activity were significantly elevated in normotensive subjects who had parents with hypertension compared with matched normotensive subjects who had parents with normotension. It is interesting that these increases in neuroendocrine levels occur before the development of high blood pressure and that hypertension-prone patients with significantly elevated norepinephrine and angiotensin II levels can be absolutely normotensive. These findings suggest that the hypertensive effects of these hormonal systems are not entirely due to their vasoconstrictor properties but may also result from their influences on the structure and function of cardiovascular smooth muscle.

COMPARISONS OF SUBJECTS WITH NORMOTENSION WHO HAVE THE HYPERTENSION SYNDROME WITH SUBJECTS WITH HYPERTENSION

Convincing data suggest that many of the components of the hypertension syndrome precede the onset of high blood pressure. Furthermore, normotensive subjects who are prone to developing hypertension (by virtue of a strong positive family history of hypertension) have significantly more cardiovascular risk factors than do matched normotensive subjects without a family history of hypertension and thus are more likely to develop cardiovascular disease. The question arises, how do subjects with normotension who have a family history of hypertension (who are very seldom treated) compare with subjects with hypertension (who are usually treated) in terms of cardiovascular risk factors?

In a recent study, we demonstrated that when comparing cardiovascular risk factors in patients who have normotension with a family history of hypertension with patients who have hypertension (matched for age and body mass index) with and without a family history of hypertension, there were no differences in plasma levels of insulin, norepinephrine, and cholesterol or in renin activity. There also were no differences in insulin sensitivity, microalbuminuria, or systolic blood pressure response to exercise. All three groups, however, were significantly worse off in each of the parameters mentioned than was the control group (normotensive subjects without a family history of hypertension) (Figure 1).

In terms of cardiovascular risk, the “normotensive hypertensive” subjects (who are not treated) have a cardiovascular risk factor profile similar to that of the subjects with hypertension (who are treated to protect them from developing cardiovascular disease). Therefore, the two groups are at similar risk for cardiovascular disease, the only difference being that the normotensive subjects have not yet developed high blood pressure, which seems to be a late manifestation of this disease process. As blood pressure measurement is universally used to identify patients with the hypertension syndrome, to initiate treatment that will protect them from developing heart disease, it is possible that we are treating these patients too late in the disease process. If we were to identify and treat these patients earlier in the disease process, before they develop high blood pressure, then we might have a bigger impact on the course of the disease and might protect them from developing high blood pressure and perhaps thereby protect them from developing heart disease.

It is conceivable, although by no means proved, that the hypertension syndrome is reversible before the onset of high blood pressure and that the development of high blood pressure is a marker of irreversible vascular disease, after which we can only control the disease. Evidence for this statement is the fact that early in the disease process, aerobic exercise frequently reverses many of the cardiovascular risk factors associated with hypertension and may prolong or prevent the onset of high blood pressure. This is not the case in hypertension that is not weight-induced. In addition, studies investigating patients with controlled hypertension have demonstrated that cardiovascular disease is more common in these patients than in age-matched, gender-matched normotensive subjects, suggesting that there is more to hypertension than high blood pressure.

FROM HYPERTENSION TO HEART DISEASE

What is the bridge between the cardiovascular risk factors associated with hypertension and the development of heart disease?

Newly developed techniques for measuring arterial compliance have shown that when subjects with hypertension are compared with matched subjects with
normotension, the hypertensive subjects have significant decreases in the compliance of both the proximal and distal arterial systems (stiff vessels). This stiffness is usually a result of proliferation and hypertrophy of the vessel wall media as well as the laying down of collagen and other connective tissue elements in the media. These changes also seem to be associated with disruption of the protective endothelial surface of the blood vessels.

It is also becoming evident that atherosclerotic plaques do not develop in normal vessels. The vascular changes seen in patients with hypertension provide the environment required for the early formation and development of atheromatous lesions. In a study using intra-arterial measurements of arterial compliance, we demonstrated that the changes in stiffness of both the proximal and distal vessels typically seen in patients with hypertension precede the onset of overt high blood pressure and that the majority of changes in the vessels occur during the period between normotension and the onset of borderline hypertension (Figure 2). Once high blood pressure occurs, only minimal changes take place in the compliance (stiffness) of the proximal vessels and no changes in the compliance of the distal vessels. Therefore, these data would suggest that maximal changes to arterial structure and function in patients with hypertension actually occur before the onset of high blood pressure and that the changes are not really being caused by the blood pressure but rather by other factors.

In normotensive subjects with abnormal compliance, we have demonstrated a strong and significant inverse correlation between arterial compliance and plasma levels of norepinephrine, cholesterol, and insulin, as well as plasma renin activity. This would suggest that these neurohormones, which are powerful growth factors, appear to play an important role in the structural and functional changes of the arteries before the onset of high blood pressure (Figure 3). Furthermore, it is believed that stiff vessels actually cause increases in blood pressure. Thus, patients with hypertension syndrome may inherit abnormalities of neurohormonal function. Over time, the growth effects of these hormones will alter vascular compliance by causing smooth muscle cell hypertrophy and connective tissue deposit. This activity has a dual effect: It creates an environment for development of atheromatous plaques and possibly cardiovascular disease, and it increases arterial stiffness, resulting in increased blood pressure.

Therefore, the development of elevated blood pressure and atheromatous disease may occur simultaneously (Figure 4). In some patients, cardiovascular disease may develop before the onset of high blood pressure.
pressure, and some patients may have a cardiovascular event before the onset of high blood pressure. Once high blood pressure does occur, it appears to potentiate the arterial changes, worsening compliance and providing a more suitable environment for atheromatosis, perhaps increasing the rate of its development.

For these reasons, important benefits can be derived from reducing blood pressure, even in patients with advanced disease. The maximal benefit most likely would be derived in patients treated with drugs that not only reduce blood pressure but also have a beneficial effect on vascular structure and function.

**SUMMARY**

Increasing data suggest that in many patients, high blood pressure may be a late manifestation of a complex inherited syndrome of cardiovascular risk factors. Moreover, patients with this hypertension syndrome may develop cardiovascular disease before the development of high blood pressure. High blood pressure may represent a late phase of the disease process, indicating advanced or even irreversible vascular damage, and to have a real impact on these patients, treatment would have to be started before the onset of the increase in blood pressure, to prevent this increase and thereby decrease the incidence of heart disease.

The problem is that blood pressure measurement is the tool used to identify patients with the hypertension syndrome. Thus, we may be missing the boat. We need to investigate tools that will help identify patients early in the course of the disease. One possibility is the use of noninvasive measurements of arterial compliance, which in most patients appears to become abnormal years before the onset of the increase in blood pressure.

Another dilemma is the approach to treatment of these patients. Exercise and diet clearly are beneficial and often may be the only modality required in some patients. But in others, early intervention with drugs such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and peripheral α-blockers may help reverse the disease and perhaps prevent the onset of high blood pressure.

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