ADVANCES IN HYPERTENSION

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A HIGH prevalence of hypertension exists in most countries of the world. A relatively small number of cases, probably less than 5%, is due to diseases of the kidneys, adrenal glands, or aorta. The vast majority of cases are due to essential hypertension, a disorder of undetermined etiology. Essential hypertension is believed to have a genetic component. This conclusion is supported by its occurrence in families, a higher incidence in certain population groups, such as blacks, and the development of animal models that become hypertensive spontaneously. A number of working theories are under investigation in attempts to uncover the etiology of essential hypertension. Two theories are receiving particular attention at present, these attribute to the etiology of hypertension respectively to disorders of the central nervous system or of the kidney.

Pathogenesis

Several lines of evidence link a disorder of the central nervous system to the pathogenesis of hypertension. It is known that if a lesion is produced in the nucleus tractus solitarius, malignant hypertension follows. Additionally, the spontaneously hypertensive rat has been found to have increased discharge of the central nervous system when aroused, even before the development of hypertension. Studies in humans have shown that the heart rate, cardiac index, and rate of ejection from the left ventricle are elevated in many cases of early essential hypertension. This suggests that some factor, perhaps inadequately regulated discharge of the central nervous system, is driving the circulation in an inappropriate manner. Plasma norepinephrine has been measured in patients with essential hypertension but has only been found to be elevated in the minority of patients. Another line of evidence stems from the observation that population groups subjected to increased psychogenic stress, such as air traffic controllers, have a higher prevalence of hypertension than groups who are not similarly stressed. Finally, it has been observed for decades that drugs which block the sympathetic nervous system, at various points, reduce blood pressure in hypertensive patients.

Abnormal regulation of intravascular volume by the kidney is a second topic under investigation as a possible cause of essential hypertension. Studies around the world, involving several population groups, have shown that the prevalence of hypertension is higher in those groups that habitually follow a high sodium intake. However, in northeast Japan, where sodium intake averages around 435 mEq a day, only 40% of the population is hypertensive. Thus, some individuals are sensitive to the effects of sodium while others are not. It has been speculated that certain individuals are born with a kidney that is incapable of excreting the amount of sodium consumed in most western countries, around 150 mEq per day. As a result of this failure to excrete sodium, extracellular fluid volume expands, which in turn prompts the release of an inhibitor of sodium-potassium adenosine triphosphatase (Na,K-ATPase) into the circulation. It has been proposed that this release occurs in order to prevent the resorption of sodium filtered by the glomerulus, thus allowing sodium to exit the body. However, chronic release of such a compound would result in inhibition of sodium-potassium exchange mechanisms in the cells throughout the body, including those in vascular smooth muscle. As a result, sodium concentration would rise within vascular smooth
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Muscle cells. Some of the sodium then leaves the cells through exchange with calcium by a sodium-calcium exchange mechanism, resulting in increased cytosolic concentrations of calcium. This, in turn, would enhance interaction between actin and myosin, increase vascular tone, raise vascular resistance, and account for essential hypertension.5

My colleagues and I have investigated the problem of sodium sensitivity in humans and have found that vascular resistance is indeed abnormally elevated in such individuals, even those who are not yet hypertensive.6 Whether this is due to elevated levels of Na,K-ATPase inhibitors remains to be studied.

Treatment

Even though the etiology of essential hypertension is not understood, we have known for some time how to treat hypertension successfully. A widely used, therapeutic program was recommended by the Joint National Committee on the Evaluation, Detection, and Treatment of Hypertension in the 1970s.7 This approach, stepped-care therapy, involved the sequential use of submaximal doses of antihypertensive medications of different mechanisms of action. This approach offered two advantages. First, it allowed physicians to add the antihypertensive effects while avoiding the side effects associated with the use of larger doses of any of the agents singularly. In addition, stepped-care encouraged the use of second step agents that blunted the compensatory response to the first step antihypertensive agent. For example, the use of a diuretic agent results in a fall in plasma volume, a decrease of cardiac output, and a fall in blood pressure. This, in turn, prompts activation of the baroreceptor reflex and the renin-angiotensin system which results in increased cardiac output, intravascular volume, and vascular resistance, thereby blunting the response to the initial agent. The use of an agent that blocks the sympathetic nervous system after diuretics were found to be inadequate since antihypertensive monotherapy prevents, in part, this compensatory response. Stepped-care was also tested in large scale placebo-controlled trials conducted by the Veterans Administration and was found to result in a decrease in cardiovascular mortality, particularly that due to strokes, congestive heart failure, and renal failure.8 Therefore, the approach was proved to cause more good than harm. However, with further experience, it was noted that any of the agents given singularly did not control blood pressure to satisfactory levels in more than 50% of the patients studied. As a result of new studies, suggesting that certain population groups are more likely to be controlled by specific antihypertensive agents, the Joint National Committee, in its 1984 report, suggested that it was appropriate to begin therapy with either a diuretic or a beta-blocker, depending on the individual patient’s characteristics.9 The 1988 Report of the Joint Commission carried matters further by recommending that therapy begins with either a diuretic, a sympathetic blocking agent, a calcium channel-blocker, or an angiotensin-converting-enzyme inhibitor.10 This allows practicing physicians to determine which of the four options is appropriate for the management of an individual patient.

Another innovation of the 1988 report focuses on the use of nonpharmacologic approaches to control blood pressure, either as the sole treatment of mildly hypertensive patients or as adjunctive treatment in those with more severe diseases.10 Those modalities that have found to be useful include weight reduction, dietary sodium restriction, regular aerobic exercise, modification of alcohol intake, and various relaxation techniques. Additionally, control of other cardiovascular risk factors, such as hyperlipidemia and cigarette smoking, was recommended to lower the overall cardiovascular risk associated with a given level of blood pressure elevation.

Plasma Renin Activity

Many of the patient's characteristics that help the physician to decide on the initial agent to use in the treatment of hypertension are based on the patient's plasma renin activity, although renin need not always be measured in order to make these decisions. Several investigators have found that plasma renin activity varies more widely among hypertensive patients than among normotensives.11 Approximately 30% of hypertensives have plasma renin activity that is lower than normal for a given level of sodium intake, while 15% are higher than normal. Low plasma renin activity suggests expanded intravascular volume, for example, patients with primary aldosteronism.
High plasma renin activity implies that elevated angiotensin 11 levels are maintaining hypertension through vasoconstriction, as in patients with malignant hypertension or renovascular hypertension. It has been found that black hypertensives are more likely to have low plasma renin levels than white hypertensives, and older hypertensive patients are more likely to have low plasma renin activity than younger hypertensive patients. Because therapeutic agents are available to correct unusually high or low plasma renin levels, the effects of diuretics, beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, and calcium channel-blockers have been tested in various population groups.

The Veterans Administration conducted three trials comparing various diuretics, which should correct the volume expansion in low renin hypertension, with beta-blockers which block the release of renin in hypertensives with higher plasma levels. One such trial found that 71.3% of black hypertensives were controlled with hydrochlorothiazide as monotherapy while only 53.3% were controlled with beta-blockers. In contrast, 55.3% of whites were controlled with diuretics while 61.7% were controlled with propranolol. 12

Angiotensin-converting-enzyme inhibitors, which prevent the formation of angiotensin 11, have been compared for antihypertensive efficacy in white and black patients. White patients have been found to respond with a greater decrease in blood pressure for a given dose than black patients.

Investigators in Basel, Switzerland, have compared the effects of beta-blockers and calcium-blockers in patients with high and low renin activity, finding that beta-blockers were much more effective in those with high plasma renin activity whereas calcium-blockers were much more effective in those with low plasma renin activity. B It has been suggested that the efficacy of calciumblockers in low renin hypertensives lies in the fact that these ~ossibly volume-expanded individuals have relatively high circulating levels of Na,KATPase inhibitors and, as a consequence, high intracellular concentrations of calcium. The comparative efficacy of calcium- and beta-blockers has also been studied in patients classified by age. Beta-blockers were found to control blood pressure elevations satisfactorily in approximately 75% of individuals under the age of 40 whereas only 25% of those over the age of 60 were similarly well controlled. In contrast, the calcium-blockers controlled blood pressure in almost 95% of hypertensive patients greater than 60 years of age, whereas adequate control was achieved in only 25% of those under the age of 40 which calciumblockers were used.

Thus, knowledge of a patient's age and race enables the physician to make important decisions with regard to the initial choice of antihypertensive therapy.

Other Cardiovascular Risk Factors and Antihypertensive Therapy

Another important consideration in the choice of antihypertensive therapy is based on the effects of various antihypertensive agents on other cardiovascular risk factors. A number of epidemiologic studies have shown that hypertension is associated with an increased incidence of coronary heart disease, atherothrombotic brain infarction, congestive heart failure, and intermittent claudication. All of the major placebo-controlled trials of antihypertensive therapy have shown a significant reduction in the mortality due to stroke in patients receiving stepped-care antihypertensive therapy. However, even though most trials have shown a reduction in mortality from coronary heart disease, in many cases the reduction has not been statistically significant and not sufficiently great in magnitude to correct the increased incidence of coronary disease in hypertensive patients. One possible explanation for this disappointing result is the fact that many commonly used antihypertensive agents cause an increase in plasma low-density lipoprotein (LDL) cholesterol and triglycerides, notably the thiazide diuretics. While beta-blocking agents do not result in elevated LDL levels, they do result in elevated triglyceride and decreased high-density lipoprotein (HDL) cholesterol levels, thereby, lowering concentrations of a cardioprotective fraction. It is a distinct possibility that lowering blood pressure can reduce the incidence of strokes by preventing brain hemorrhage, while at the same time, elevation of plasma cholesterol level cancels the beneficial effect of lowering blood pressure on the progression of coronary atherosclerosis. Unfortunately, many of the newer antihypertensive agents do not have a potentially unfavorable effect on plasma lipid.
levels. Centrally-acting agents lower LOL and HDL levels, alpha-blockers lower LOL levels while leaving HDL levels unchanged or even increased, and angiotensin-converting-enzyme inhibitors and calcium channel-blockers have been found to be lipid-neutral, having no effect on LDL, HOL, or triglyceride levels. 14

Another possible explanation for the failure to observe the expected reduction in coronary heart disease mortality in patients receiving antihypertensive therapy is the possibility that certain forms of antihypertensive therapy might increase the risk of sudden death in certain susceptible individuals. The Multiple Risk Factor Intervention Trial results suggested that hypertensive men with abnormal baseline electrocardiograms who received aggressive diuretic therapy had a higher mortality rate than those individuals who received treatment from their usual source of medical care.15 While this difference was not statistically significant, it has led to a re-evaluation of the effect of diuretic therapy on plasma potassium levels as hypokalemia is known to enhance cardiac irritability. While, on the average, diuretic therapy results in a relatively unimpressive fall in plasma potassium levels, the higher the dose of diuretic used, the greater is the incidence of hypokalemia. Thus, certain susceptible individuals lose more potassium than others for a given dose of diuretic. While data are still conflicting, a number of studies have shown that as plasma potassium levels fall, the frequency of multifocal ventricular premature beats increases as does the prevalence of complex ventricular activity such as couplets, bigeminy, and R on T phenomenon. 16 It is now the practice of many physicians to limit their use of diuretic agents to relatively small doses of diuretic, for example, 12.5 to no more than 50 mg of hydrochlorothiazide a day, with careful monitoring of potassium levels, and appropriate treatment with potassium supplements or potassium-sparing agents, for those patients whose potassium levels fall, particularly those with evidence of organic heart disease.

In the future, the relative effect of antihypertensive agents on left ventricular hypertrophy may also influence the initial choice of agent. As blood pressure rises, the ventricular musculature increases in size so as to normalize the stress per unit mass during each cardiac contraction. With time, this physiologically adaptive process becomes pathologic and appears to increase the risk of cardiovascular death. The prevalence of left ventricular hypertrophy in a given population varies with the method used to detect hypertrophy. Whereas the electrocardiogram or chest x-ray might reveal hypertrophy in less than 10% of the population, echocardiographic examination of the same patients reveals a prevalence approaching 50%. The Framingham study has shown that overall mortality increases in individuals with electrocardiographic hypertrophy, the increase being particularly marked in those with ST segment changes.17 Additionally, the incidence of sudden death is higher in patients with left ventricular hypertrophy, particularly those with repolarization abnormalities. Ambulatory electrocardiographic monitoring of patients with hypertrophy has shown a greatly increased prevalence of ventricular ectopy over a 24-hour period. In addition, a number of studies has shown decreased coronary reserve, i.e., an inability to increase coronary blood flow as myocardial metabolic demands increase in response to exercise or stress.19 These three factors: decreased coronary reserve, increased prevalence of premature ventricular contractions, and increased risk of sudden death may, in time, lead physicians to choose agents that promote regression of left ventricular hypertrophy as blood pressure is lowered.20 It is known that the arteriolar vasodilators, while normalizing blood pressure, may prompt an increase in left ventricular hypertrophy. Similarly, diuretics control blood pressure without reducing hypertrophy. This could be explained by the fact that both vasodilatation and volume depletion stimulate release of catecholamines and angiotensin II which both have a hormonal effect, stimulating hypertrophy. The centrally-acting alpha agonist agents, the angiotensin-convertingenzyme inhibitors, beta-blockers, and certain calcium-blockers have been reported to allow regression of hypertrophy. However, at present it is not known whether regression of hypertrophy is associated with improved survival in hypertensive patients. This continues to be a very important area for future study.

**Conclusion**

In summary, although the matter of choosing the initial hypertensive therapy for patients has
become more complex as a result of new information, the same information now makes it possible to apply rational criteria to the choice of antihypertensive agents. In my opinion, choice should be based on the patient’s age, race, the dominant mechanism of the hypertension, the severity of the hypertension, and the price of the agent. Other important considerations include frequency of dosing and the side effect profile of the agent.

References