Hypertension, or high blood pressure, is a clinical disease with a prevalence sufficiently high in acculturated societies to warrant it being designated a serious public health problem. Epidemiological and actuarial statistics reveal that premature cardiovascular morbidity and mortality are directly related to the level of diastolic blood pressure as well as to the level of systolic blood pressure.

Depicted in Figure 1 are data from the Framingham Heart Study, which involves a cohort of men and women derived from the community of Framingham, Massachusetts, on whom a variety of cardiovascular data have been collected since 1949. In this particular subset of the Framingham cohort of men and women, 55–64 years old, cardiovascular risk is directly related to level of blood pressure.

Notice that, unlike other diseases where the patient clearly either does or does not have the disease, blood pressure is distributed normally or unimodally. The higher the diastolic blood pressure, the higher is the risk of premature cardiovascular death. The same is true for systolic blood pressure. Thus, high blood pressure is not only a disease but a risk factor as well.

Ironically, although the aggregate data would suggest that patients with mild hypertension (diastolic blood pressure, 90–104 mm Hg) have a low risk of death, it is from this group, because there are so many subjects within this sector of the blood pressure distribution, that the majority of the cardiovascular morbidity and mortality derives. Thus, both the disease and the risk factor of hypertension require careful management.

Risk Factors for Hypertension

It has been fairly well established that there are certain risk factors that increase the probability of developing hypertension. That does not mean that everyone with one or a combination of these risk factors will definitely become hypertensive, but the probability of becoming hypertensive is substantially greater than in subjects without such risk factors.

The first risk factor is excess sodium ingestion. In the past, many researchers and physicians had a fairly unambiguous idea of the relation between excess dietary sodium and blood pressure. Simply put, excess sodium led to high blood pressure. Now, understanding the relation between excess dietary sodium and blood pressure is more complicated and more controversial than ever before. It appears that approximately one fourth of normotensive subjects and approximately one half of hypertensive patients have what is characterized as sodium sensitivity, meaning that excess sodium in their diets increases their blood pressures.

Obesity is another fairly important risk factor for the development of hypertension. Indeed, in the...
United States, national data suggest that 16% of the normotensive population is obese, whereas 44% of the hypertensive population is obese. Conversely, 53% of obese subjects are hypertensive as compared with 22% of nonobese subjects.

Although most of the data surrounding sedentary lifestyle are cross-sectional and retrospective in nature, there seems to be a fairly clear association between sedentary lifestyle and high blood pressure. When the probability of sedentary subjects developing hypertension is compared with that of physically active subjects, the sedentary subjects have a relative risk of approximately 1.4 for hypertension developing.

Finally, there are several studies supporting the contention that excess alcohol ingestion increases blood pressure. The earliest of these studies are surveys indicating that blood pressure increases in direct proportion to the number of alcoholic drinks consumed per day. Now, there are also experimental data to support this contention.

Predictors of Hypertension

In addition to the risk factors already referred to, it is important to identify markers of hypertension that will allow prediction of those in whom hypertension could develop, even in advance of the increase in blood pressure. Such predictors, it is hoped, would allow for the early identification and targeting of “at risk” individuals for therapeutic or, preferably, preventive interventions. It is emphasized, however, that because of the pathophysiological heterogeneity of hypertension, it is unlikely that there will ever be a single predictor capable of differentiating perfectly between normotensive persons destined to remain normotensive and those destined to develop hypertension.

Predictors of hypertension can be conceptualized according to demographic, clinical, genetic, challenge response, and laboratory predictors. Some of these predictors are currently available and others are yet to be developed.

Demographic Predictors

Regarding demographic predictors, because in nonacculturated societies blood pressure does not tend to increase with age, it seems that there is some characteristic or a combination of characteristics of the acculturation process that cause blood pressure to increase with age. Thus, in our society, age is a predictor of increase in blood pressure. Regarding gender, younger men have higher blood pressures than younger women, however, older men have lower pressures than older women.

With respect to race, blacks in the United States have a 38% prevalence of hypertension as compared with whites in whom the prevalence is 29%.

Clinical Predictors

Adults. In adults, heart rate has some predictive value with respect to the development of hypertension. In research on borderline hypertension and, in particular, on subsets of patients with hyperdynamic circulations, it seems that these subjects have a higher than expected probability of essential hypertension.

As previously mentioned, weight, especially centrally distributed obesity, tends to be a fairly potent predictor of high blood pressure.

Future research on clinical predictors will center around which demographic, historical, and physical examination features physicians should focus on that would signal the need for more in-depth laboratory evaluation of biochemical markers (e.g., hormones, enzymes, and cationic transporters) as well as other types of laboratory measurements (e.g., echocardiogram and noninvasive vascular imaging studies).

Children. Regarding clinical predictors pertinent to children, blood pressure, itself, is a fairly potent predictor of what blood pressure is likely to be later in life, as is pulse. In the pediatric literature, there are data suggesting that a tracking phenomenon operates wherein some children tend to maintain
specific levels of blood pressure distribution relative to their peer group as they age. Further research into this tracking phenomenon suggests that tracking is not so much a function of age as it is of rate of growth. Nonetheless, children's blood pressures appear to be related to their blood pressures at later ages with correlations for systolic blood pressure in the range of 0.10-0.75 and correlations for diastolic blood pressure in the range of 0.02-0.60.

Left ventricular mass, although frequently the result of uncontrolled blood pressure in adults, has been found to add significantly to the prediction of future blood pressure in children, with those children with the highest left ventricular mass having the greatest probability of developing higher blood pressures in the future. Similarly, as is the case with adults, weight is a potent predictor of blood pressure, and excessive weight gain during the adolescent years is particularly predictive.

Future research in the area of childhood predictors of hypertension will center around refinement of current predictors, development of better laboratory predictors, including investigations of hormonal predictors such as insulin and cationic transporters such as sodium-hydrogen antiporter, and integration of these blood pressure-related predictors with other predictors of diseases having origins that might very well be in childhood, such as hyperlipidemic states and atherosclerosis.

Genetic Predictors

In addition to family history, molecular biological markers or predictors of hypertension are increasingly being recognized as valid. Reverse genetics, wherein research commences at the level of the genome and proceeds to the disease, combines the technology of restriction fragment length polymorphisms (RFLPs) with genetic linkage analysis to identify genetic markers and the genes involved in disease development. Phenotypic abnormalities traceable to a single gene mutation tend to cosegregate with these genetic polymorphisms so that the polymorphisms or RFLPs can be used as genetic markers even if they are not causally responsible for the phenotypic expression of the disease to which they are linked.

The major stumbling block to progress in this area at the moment is difficulty in precisely defining hypertension-related phenotypes. The application of the aforementioned molecular biological approaches to the development of genetic markers assumes the existence of phenotypes that are bimodally distributed. Because in human populations blood pressure is unimodally rather than bimodally distributed, it cannot be used as a phenotype. There are, however, examples of bimodally distributed, hypertension-related phenotypes such as modulating and nonmodulating sodium sensitivity. It is also encouraging to note that RFLPs for the renin gene have recently been identified in animal models of hypertension.

Thus, RFLPs are among the most promising of the future hypertension predictors, not solely because of their potential for forecasting risk, but also because they can frequently serve as effective entries to more in-depth pathophysiologic studies.

Challenge–Response Predictors

Challenge–response predictors represent a unique approach to predicting who is likely to develop hypertension, and a classic example is a sodium challenge. Unfortunately, this is not very practical because hypertension affects millions of people, and there is not yet any practical marker of sodium sensitivity.

Regarding an exercise challenge, there are a few small studies in normotensive subjects that suggest abnormally high blood pressure responses to exercise might be predictive of a higher subsequent incidence of hypertension. Stress, too, can increase blood pressure, and like exercise, it raises blood pressure in everyone. There are, however, some data to suggest that hypertensive patients and, perhaps, those destined to develop hypertension, have a greater than expected increase in blood pressure when challenged with a simple computerized video game or when they are asked to solve fairly simple mathematical problems. Also, there are data suggesting that in black children there seems to be an interaction between stress and sodium sensitivity such that the combination of being black, on a high salt diet, and being exposed to stress produces higher than expected increases in blood pressure. These might turn out to be predictive of the development of hypertension in black children and might, at least partially, explain why hypertension seems to be so much more prevalent and more lethal in the black population in the United States as compared with the white.

Future research on challenge–response predictors is likely to explore mechanisms in more depth and to consider other potentially confounding variables.

Laboratory Predictors

Finally, there is the concept of laboratory predictors of hypertension. Again, the hope here has been and continues to be that simple laboratory tests might help predict in advance of the rise in blood pressure who, in fact, is at risk for the development of hypertension.

A lot of excitement has centered around cation transporters, not only because they might make good predictors of hypertension subsets, but also because of their potential for mechanistic implications in explaining the pathophysiology of hypertension. To date, this has not turned out to be the case in terms of a perfect cationic transporter that clearly discriminates between normotensive and hypertensive subjects although sodium-lithium countertrans-
port has come the closest, at least in the white population.31

Hormones represent another approach to the development of laboratory predictors of hypertension. Particularly interesting is insulin and insulin resistance, which might be related to the hypertensive process and might have the potential for screening for cardiovascular disease before hypertensive blood pressure levels become evident.32

Current research on biochemical predictors of hypertension is very intense and likely to become more complex as more information is gained about genetic and environmental influences exerted on both the predictor and the blood pressure. Current front runners as predictors of hypertension that are likely to receive additional attention are the cationic transporters, not only sodium-lithium countertransport but also sodium-hydrogen antiporter, which might be synonymous with or a variation of the sodium-lithium countertransporter. Regarding other laboratory predictors, insulin is likely to command more attention in the future, not only as a predictor but especially with respect to the role it might be playing in the pathophysiology of hypertension.

Conclusions

The preceding is a brief synopsis of the “big picture” of hypertension and considers the implications of a clinical disease with a prevalence so high it is being referred to as a public health problem. Although investigations on basic mechanisms and therapeutic advances in the treatment of extant hypertension need to be continued, other cardiovascular research will continue trying to separate genetic from environmental influences on blood pressure, with the objective of developing better predictors of hypertension. Improved predictors of hypertension will have use in research as well as in the clinical world of patient care and preventive medicine, where it is hoped that early intervention will reduce hypertension-related morbidity and mortality.

References


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