Editorial Comment

Inheritance of Hypertension and Blood Pressure Reactivity

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Although there is general agreement that there is a strong genetic component to essential hypertension, it is not clear exactly what is inherited. A popular but largely unsubstantiated view is that sustained hypertension may be preceded by a period of increased reactivity to noxious stimuli. In this issue of Hypertension, Ravogli et al provide important new data to help resolve this question. By using four different tests of blood pressure reactivity, they found that normotensive young adults with one or both parents hypertensive do not show any increased reactivity when compared with subjects with normotensive parents, although they did show slightly higher blood pressures during casual measurement and 24-hour monitoring, with a proportional increase in left ventricular mass.

The reactivity hypothesis was first proposed more than 50 years ago by Hines and Brown, who claimed that "prehypertensive" individuals show an exaggerated pressor response to a cold pressor test. In its stronger form, this hypothesis states that increased reactivity plays a causal role in the development of hypertension and that the repeated transient pressor episodes the increased reactivity engenders eventually lead to a sustained elevation of pressure. In its weaker form, the hypothesis proposes that the reactivity is merely a marker for future hypertension, without necessarily having any direct causal role.

A recent review of 39 studies comparing reactivity in hypertensive and normotensive individuals concluded that although the majority do show an increased reactivity, it is by no means a universal finding. If it is accepted that the positive studies outweigh the negative ones, the question is raised as to whether the increased reactivity is a cause or a consequence of the hypertension.

By studying individuals who are still normotensive but who have a family history of hypertension, it should be possible to answer this question. A review of studies of reactivity in subjects with and without a family history claimed that increased reactivity is typical of individuals with a positive family history, although several of the studies reported no difference. Since the publication of this review, the controversy has continued: of four more recent studies, two reported that blood pressure reactivity was higher in subjects with at least one hypertensive parent, whereas two others found no difference according to family history. However, both of these latter studies found that subjects with a positive family history of hypertension showed an exaggerated vasodilation of the forearm during mental stress.

One reason for this discrepancy may be that different authors have used different provocative tests for assessing reactivity. It is probably incorrect to assume that the findings based on one task are generalizable to other tasks. It has also been claimed that increased reactivity to behavioral challenges such as mental arithmetic is more characteristic of hypertensive individuals than increased reactivity to physical challenges such as exercise. The evidence of Ravogli et al appears to refute both of these claims.

Several prospective studies, most of which used the cold pressor test, have examined the prognostic significance of increased reactivity. Most have yielded negative or confounded results. A notable exception was the Precursors Study of medical students at Johns Hopkins University originated by Caroline Bedell Thomas in 1946. This was designed as a prospective evaluation of factors that might predict the development of hypertension and coronary heart disease. These included measurements of pressure made at rest and during the cold pressor test. In the first publication describing the predictive value of the reactivity testing, 78 of 1,185 individuals had become hypertensive after an interval of up to 34 years. These subjects had higher resting pressures than the rest of the cohort at the start of the study but did not show an increased reactivity. The most potent predictor of hypertension in later life was family history: subjects whose parents were both hypertensive and had a resting systolic pressure above 125 mm Hg (who would be equivalent to Ravogli's group of subjects with two hypertensive parents) had an odds ratio of 12.65 for becoming hypertensive. A subsequent analysis of 910 of the subjects, using more sophisticated statistical techniques, came to a quite different conclusion, namely that after controlling for the age of onset of hypertension, the cold pressor test...
response was an independent predictor of hypertension.11 However, when age was not controlled for, it gave no prediction, and its predictive value was only applicable to a minority of individuals who became hypertensive before the age of 45.

Another interesting finding in Ravogli's study was the association between the higher resting and ambulatory pressures in the group with a positive family history of hypertension and the lack of any concomitant increases in reactivity or variability. This provides additional evidence in support of the concept that the regulation of the tonic or baseline level of blood pressure can be independent of the regulation of blood pressure variability. If variability is measured in absolute terms (e.g., as the standard deviation) there is an increase in hypertensive relative to normotensive subjects, but when expressed in relative terms (e.g., as the variation coefficient) this difference is not impressive.12 Which of these measures is more appropriate remains a subject of debate, but it seems clear that the primary abnormality in essential hypertension is not so much an increased variability of blood pressure as it is an increase in the basal or tonic level, around which the pressure is regulated in a more or less normal fashion. This upward resetting of the diurnal profile has been noted in studies using ambulatory monitoring in normotensive and hypertensive research subjects13 and was also noted in Ravogli's study.

The finding of a subtle increase in left ventricular mass in research subjects with a positive family history of hypertension provides yet more evidence that ambulatory blood pressure correlates more closely than casual pressure with target organ damage but, like other cross-sectional studies in this area, leaves unanswered the question of the causal relation between the two. It was traditionally assumed that the increase of left ventricular mass occurs in response to the increase of blood pressure, but the truth is probably not that simple. For one thing, as Ravogli and many others have found, the correlation between left ventricular mass and average blood pressure is never very close, even when using ambulatory pressure. The influence of nonhemodynamic growth factors on left ventricular mass is now well established,14 and volume factors may also be important.15 Furthermore, there is some intriguing evidence that an increase of left ventricular mass may actually precede a detectable increase of blood pressure,16 and it is probable that left ventricular mass can be genetically determined independently of blood pressure.17

The origin of this resetting remains a matter of controversy and speculation. Possible candidates are the central nervous system, the kidneys, and the arteries. A popular view of the early stage of essential hypertension is that it is associated with a subtle tonic overactivity of the sympathetic nervous system. Evidence for this is provided indirectly by the frequent observation of an increased cardiac output and heart rate in some patients with borderline hypertension.18

The fact that Ravogli et al1 did not observe any difference in heart rate in their three groups of subjects does not exclude this as a possible mechanism, however. A more direct measure is obtained by recording muscle sympathetic nerve activity, which shows a tonic increase in young patients with borderline hypertension19 but a normal response to reactivity testing.20 These findings thus parallel the observations of Ravogli et al1 on blood pressure. Another early manifestation of essential hypertension is resetting of the arterial baroreceptor reflex to maintain normal short-term fluctuations of pressure at a slightly higher tonic level, which may in part be attributable to increased stiffness of the carotid arteries.21 This has been postulated to occur as a result of structural changes in the resistance vessels, which can be demonstrated as an impaired forearm vasodilator capacity, both in subjects with borderline hypertension22 and in normotensive subjects who have a family history of hypertension.23 Yet another early abnormality is a decrease in venous distensibility.24

The inheritance of hypertension is almost certainly polygenic, so that it is unlikely that a single physiological derangement is responsible. The structural changes that have been noted in the study of Ravogli et al and other studies in the heart, resistance, and capacitance vessels could all contribute to the resetting of the tonic control of blood pressure that Ravogli et al observed in subjects with a family history of hypertension. Whether these changes are initiated by the sympathetic nervous system is an interesting possibility that remains to be established by further work.

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