Editorial Commentary

Aging and Systolic Hypertension
Cluster Patterns and Problem-Solving Strategies to Answer the Genetic Riddle

Joseph L. Izzo, Jr

In this issue of Hypertension, Abraham Aviv1 provides a hypothetical approach to the deeply intertwined relationship between hypertension and aging in humans. He describes existing evidence for 3 different hypotheses that might explain why blood pressure increases with age: the “fetal origin hypothesis,” which holds that a disorder of intrauterine growth, such as low birth weight, leads to abnormalities in later life; the theory of “antagonistic pleiotropy,” which suggests that there was an evolutionary advantage to the hypertension phenotype because of natural selection of favorable traits closely linked to hypertension; and the theory of “telomere dependency,” which holds that accelerated loss of telomeres (specific TTAGGG base pair sequence repeats at the terminal ends of mammalian chromosomes) limits cellular repair processes and causes vascular aging, stiff blood vessels, and systolic hypertension.

To fully appreciate the nature of the problem under discussion, it may be wise to review the clinical impact of aging on blood pressure. In industrialized societies, there is a very steady age-related increase in systolic blood pressure, whereas diastolic pressure increases steadily until the sixth decade of life and then declines.2 We are finally realizing that this complex age-related behavior of diastolic pressure significantly clouds the clinical definition of hypertension and that a clearer picture is possible through a paradigm shift to systolic blood pressure as the more important end point in diagnosis, risk stratification, and therapy of hypertension.3

The graphic representation of the complex relationship between aging and blood pressure in humans2 should be prominently featured on posters at the walls of genetic laboratories as researchers strive to find genotypes that lead to essential hypertension. Next to that poster should be a reminder that many of the “intermediate phenotypes” in hypertension change with age. From a vascular biology perspective, a telomere-like hypothesis is attractive because age-related increases in systolic pressure occur at an earlier age and are more severe in hypertensive individuals, suggesting an apparent acceleration of normal chronological aging in hypertensive persons. Whether telomere length or either of the other 2 alternatives explains the process of accelerated vascular stiffness in hypertensives is unclear, however, and much further investigation is required before the concept can be directly applied to hypertension.

From the perspective of this reviewer, the significance of the article by Aviv1 is that it underscores the need to consider aging and blood pressure individually and as interactive variables that require interpretation in the context of a large number of other factors that could modify them individually or combined. As stated by Aviv,1 the implications of these aging hypotheses “serve to draw a critical distinction between biological age (aging) and chronological age and thereby offer an answer to a question that presently matters most in the field of hypertension: why has it been so difficult to disentangle the genetic components of essential hypertension and to identify the variant gene responsible for elevated blood pressure in a large segment of the human population?”

If it is true that aging, hypertension, and their interaction must be considered simultaneously in advance of the development of the “ultimate” age-dependent phenotype of systolic hypertension, then how will genetic studies be feasible? Under these circumstances, any candidate cardiovascular genetic marker must be simultaneously “linked” to the intermediate phenotypes present at the time of measurement and to the risk of developing different phenotypes (eg, stiff blood vessels or systolic hypertension) in later life. The daunting problem of solving this riddle can be approached most rationally and efficiently by taking the clinical perspective first. The hypertension phenotype is probably best viewed as a constellation or cluster of individual phenotypes. A reasonable assumption is that the study of these clustered traits (individual phenotypes) will more useful in the identification of critical elements of the genetic profile of hypertension than would be the study of the individual phenotypes themselves. With this assumption, it should be possible to match clinical subpopulations of hypertensives with the phenotypic clusters they represent. Because of the aging influence, it will also be necessary to study younger populations who are at risk of developing systolic hypertension.
If this approach proves to have value, complex phenotype clusters may be useful to study first. For example, aging is associated with a progressive increase in aortic stiffness and pulse pressure, of which both occur more commonly in individuals who inherit the C allele of the angiotensin II type 1 (AT₁) receptor. However, plasma renin activity decreases with age, whereas obesity and insulin resistance increase with age. Normotensive offspring of hypertensive parents have been found to have increased cardiac output, wide pulse pressures, and microcirculatory derangements, including capillary rarefaction and punctate hemorrhagic lesions that are indistinguishable from diabetic microaneurysms. Capillary rarefaction and abnormally heterogeneous capillary flow have been proposed as causes of insulin resistance, and abnormal heterogeneity of renal glomerular perfusion has been suggested as a cause of inappropriate hyperreninemia. ACE inhibitors can partially ameliorate the syndrome of insulin resistance and reduce the impact of renal glomerular capillary rarefaction (ie, diabetic glomerulosclerosis) on the progression of end-stage renal disease. This pattern of syngnostic observations thus “links” macrovascular and microvascular abnormalities, metabolic abnormalities, and alterations in components of the renin-angiotensin system. Accordingly, profiling studies should pay particular attention to the specific genes that represent the associated phenotypes in populations at risk for the development of systolic hypertension.

It seems to be an inescapable conclusion that an effort to understand normal and abnormal cardiovascular aging must be undertaken in parallel with our attempt to elucidate the mechanisms of essential hypertension. By keeping our eyes wide open to the age-related patterns of traits or phenotypes in identifiable at-risk individuals, we may be able to take advantage of the pleiotropic nature of the syndrome of essential hypertension in a way that makes genetic association studies more focused and specific. In this complex setting, the existence of parallel abnormalities in physiologically related systems actually increases the likelihood that any genetic associations that are found will have biological significance. The redundancy of such associations in multiple tissues and in different clinical subpopulations will further strengthen the evidence that a particular candidate gene or gene cluster is important. The fact that intermediate pheno-types change with age is yet another critical dimension that must be considered in the design of a strategy to approach the elusive goal of describing the genotypic basis for essential hypertension.

References


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