Hypothesis

Pulse Pressure and Human Longevity

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Abstract—In exploration of the association between pulse pressure and longevity in humans, 3 hypotheses are briefly discussed: the fetal origin hypothesis, antagonistic pleiotropy, and the telomere hypothesis of cellular aging. The implications of these hypotheses serve to draw a critical distinction between biologic 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 genes responsible for elevated blood pressure in a large segment of the human population? (Hypertension. 2001;37:1060-1066.)

Key Words: aging n hypertension, essential n telomere n reactive oxygen species n menopause n evolution n genetics

Considerable knowledge has been gained during the past 2 decades about mechanisms that regulate blood pressure. However, little is known about the variant genes that cause essential hypertension in humans. Epidemiological geneticists have attributed the slow progress in deciphering genes that harbor susceptibility to essential hypertension to the fact that this disorder is an outcome of a spectrum of interactions, including interactions among genes, between genes and their protein products, and between genes and the environment. In other words, essential hypertension is a complex genetic trait. Useful though this description may be in depicting the complexity of essential hypertension, it falls short by its failure to convey an important fact, namely, that essential hypertension is in large part a disease that is linked to the aging process in humans. This is clearly applicable to the majority of hypertensive patients older than 60 years, who exhibit isolated systolic hypertension.

Hypertension—A Matter of Definition

High blood pressure is a major risk factor for cardiovascular complications and death. However, given that blood pressure is a continuously distributed variable and that complications of hypertension vary among individuals and populations, the validity of using any fixed cutoff point in blood pressure level as a criterion for essential hypertension and a justification for antihypertensive treatment is questionable from biologic and medical standpoints.1,2 The definition of essential hypertension is a matter of utmost relevance not only in terms of human biology and intervention strategies but also from economic and, therefore, political perspectives.3 Defining essential hypertension in adults as blood pressure of >140/90 mm Hg rather than, for instance, >150/100 mm Hg carries an enormous price tag, welcomed by the pharmaceutical industry and dreaded by healthcare insurers. It follows that a definition of essential hypertension, whatever it may be, is to a large extent framed by cost-benefit ratios of therapeutic intervention. From the medical standpoint, however, the end points of therapy are clear, namely, extending a healthy life-span and maintaining or improving the state of physical well-being. If so, should the same definition of essential hypertension be used, for example, for a 40-year-old man as for an 80-year-old woman? A recent communication from the Committee of the National High Blood Pressure Education Program commented on this point by unequivocally stating that the answer is in the affirmative.4 Left unanswered, however, is the question of whether systolic blood pressure of, say, 150 mm Hg represents the same biologic process in an 80-year-old woman as in a 40-year-old man.

Essential Hypertension and Human Aging

In industrialized nations, systolic blood pressure continuously rises throughout life, whereas diastolic blood pressure tends to level off or even decline in persons older than 50 years.4–7 Consequently, pulse pressure progressively increases as a function of chronological age. Supported by a vast body of epidemiological data, the focus has recently shifted from diastolic blood pressure to systolic blood pressure and, in
particular, pulse pressure as a major cardiovascular risk factor.\(^4\) Although ventricular ejection and stroke volume contribute to pulse pressure, the age-dependent rise in pulse pressure is largely determined by progressive “stiffening” (i.e., less distensibility) of central elastic arteries, which reflects the biologic aging of the arterial system.\(^7,9\) One of the tools with which to assess arterial stiffening has been the measurement of pulse wave velocity, which shows a greater increase with age in central elastic than in peripheral arteries.\(^8,9\) Given that both pulse pressure and chronological age are positively correlated with cardiovascular events,\(^4,8,12–16\) pulse pressure may be regarded as an index of arterial aging. This being the case, it is noteworthy that pulse pressure is lower in premenopausal women than in men of the same age. During the postmenopausal period, however, pulse pressure increases faster in women than men, primarily because of a more rapid rise in systolic blood pressure in women, so that by the age of 70 years pulse pressure is about the same in both genders.\(^4,17\)

In addition, cardiovascular risks associated with a high pulse pressure are not the same in men and women.\(^11,18\)

Two clear conclusions can be drawn from these findings: arterial aging has a major role in age-dependent rise in pulse pressure and the biology of aging differs between men and women. The observed gender effect suggests, in addition, that chronological age, as determined by calendar time, is distinct from biologic age, a progressive process of deterioration in the vitality of organ systems, which at the present is irreversible. Accordingly, pulse pressure or systolic blood pressure, which are primarily related to biologic aging, should be relatively refractory to treatment\(^19,20\) and associated with excess risk of death from all causes.\(^21\)

The age-dependent rise in pulse pressure is, no doubt, the price of human longevity, but what does age-adjusted, high pulse pressure mean after the exclusion of secondary causes of hypertension? A possibility that merits exploration is that in a subset of the human population, a high systolic (pulse) pressure is the outcome of a process whereby biologic age has surpassed chronological age. Interactions between the genetic script of biologic aging and environmental factors are likely to play a pivotal role in such a putative process. These interactions almost certainly commence in utero.

The Fetal Origin Hypothesis

More than a decade ago, Barker and coworkers\(^22,23\) unraveled an intriguing association in humans between cardiovascular disease and low birth weight. As noted by Barker,\(^24\) this association holds for suboptimal intrauterine growth and not prematurity; adults who were born too small for gestational age, but not those born too soon, are at risk for cardiovascular disease. Subsequent studies in the United Kingdom\(^25,26\) and elsewhere\(^27–29\) have supported this conclusion. A body of epidemiological data led Barker and colleagues to propose that diseases commonly associated with aging, including non–insulin-dependent diabetes mellitus and essential hypertension, may result from low birth weight.\(^30\)

The potential link of adult cardiovascular diseases to intrauterine growth prompted exploration of the relation between anthropometric parameters at birth and blood pressure in adulthood and during childhood. Results of numerous studies throughout the world, including longitudinal studies, suggest that low birth weight is associated with elevated blood pressure in all age groups.\(^31–33\) Most studies reported an association between birth weight and systolic blood pressure, presumably because no significant relation was found between birth weight and diastolic blood pressure. Studies that did report results of both systolic and diastolic pressures found either an inverse relation with birth weight for systolic but not diastolic blood pressure\(^34,35\) or an inverse relation with birth weight that was greater for systolic than for diastolic blood pressure.\(^36,37\) These findings indicate, therefore, that suboptimal intrauterine growth gives rise to an increase in pulse pressure during the postnatal period.

A number of studies have failed to confirm the association between low birth weight and either cardiovascular risk or hypertension.\(^38–45\) In addition, the majority of supportive reports have relied on prospective data that, as noted, might have been subject to ascertainment bias.\(^36,47\) Another unresolved matter is the mechanistic link between intrauterine growth retardation and cardiovascular disease. Barker and colleagues\(^48\) proposed that inadequate nutrition in utero, including poor placental transfer of nutrients, permanently alters the structure and physiology of the body, thereby predisposing a person to cardiovascular disease. Adequate nutrition is, no doubt, essential for normal fetal development, but the precise mechanisms by which suboptimal intrauterine growth alters cardiovascular parameters are poorly understood. Thus, although highly provocative, the fetal origin hypothesis has not been fully tested and offers few clues to the underlying predisposition of adults with low birth weight to essential hypertension and other diseases of aging. What the fetal origin hypothesis does seem to suggest is that intrauterine growth retardation results in a forward resetting of arterial age during extrauterine life. In line with this concept is the finding of an inverse relation between birth weight and aortic pulse wave velocity in adults.\(^36\)

Human Longevity and Limitations of Animal Models of Genetic Hypertension

Laboratory animals have been used extensively in gaining mechanistic understanding of a host of human diseases. However, animal models of genetic hypertension must be carefully appraised with regard to their relevance to humans, given that essential hypertension is primarily a disorder of human aging. Genetically hypertensive rats, for example, have been exploited in the search for genes that cause hypertension, based on the premise that deciphering variant genes that cause hypertension in the laboratory rat would provide clues about genes that cause essential hypertension in humans. This approach appears to be eminently sensible, except for the inherent contradictions in the use of laboratory animals with short life-spans as models of essential hypertension, a disorder in a mammalian species with the longest life-span.

The short life-span of animal models of hypertension precludes the reliable simulation of aging of organ systems, particularly the cardiovascular system, which is centrally involved in the pathobiology of essential hypertension in humans.\(^7\) Thus, the premise that hypertension in the sponta-
neously hypertensive rat or the Dahl salt-sensitive rat, for instance, mirrors essential hypertension as it exists in humans may not withstand close scrutiny. Although deciphering variant genes that cause hypertension in experiments based on animal models is a valuable exercise in blood pressure physiology, the hypertensive genes uncovered by these models might have little in common with the genes that harbor susceptibility to essential hypertension in humans.

The limitations imposed by the short life-spans of most laboratory animals on models of vascular aging in humans and misconceptions perpetrated by these models are further illustrated by the notion that vascular endothelial cells are quiescent in vivo. This concept is based on observations that the mitotic index of the vascular endothelium in rodents is \(\approx 0.1\%/d\).\(^4\) Rat vascular endothelial cells would, therefore, undergo \(\approx 1\) round of replication during the extrauterine life-span of the animals, assuming that all vascular endothelial cells are subject to an equal likelihood of cell divisions. Cellular replication may then be a minor factor in the behavior of the rat vascular endothelium during the life-span of the rat. However, a 0.1\% mitotic index extrapolated to 70 to 80 years of human life yields a considerable number of replications (\(\approx 20\) to 30) per each vascular endothelial cell, which amounts to each cell giving rise to \(\approx 10^6\) to \(10^7\) cells, a substantial cellular turnover within a human life-span. Recent research suggests that at least in segments of the vasculature, the replication of human vascular endothelial cells in vivo is substantial,\(^50,51\) a finding with significant implications for age-dependent disorders of the cardiovascular system, including essential hypertension in human beings.

**Antagonistic Pleiotropy, Human Aging, and the Menopause Enigma**

Antagonistic pleiotropy, as originally proposed by Williams,\(^52\) is an evolutionary hypothesis with important ramifications for age-dependent rise in pulse pressure in humans. The hypothesis was formulated to explain, in genetic terms, the extension of principles of natural selection, under which reproductive pressure is the defining force, to the postreproductive period. At the core of antagonistic pleiotropy is the notion of tradeoff between early and late life fitness. Kirkwood\(^53\) extended the tradeoff concept in his “disposable soma” theory, which proposes that aging is largely the outcome of investment in reproduction, diverting resources away from mechanisms of maintenance and repair of the soma. Both antagonistic pleiotropy and the disposable soma concepts are in line with the notion that the human life-span is determined by the longevity of women.\(^54,55\)

The exceptionally long postreproductive life of women is a fairly recent phenomenon on the evolutionary time-scale of humans and, like aging itself, is the ultimate outcome of the weakening force of natural selection.\(^52–55\) The tradeoff concept was recently explored in epidemiological studies that sought links between menopause and human longevity. These studies showed that women with fewer children, and particularly women who bear children late in life, as late as in the fifth decade of life, exhibit increased longevity.\(^56–58\) A potential mediator of this tradeoff is estrogen. An increase in the lifetime effect of estrogen through menstrual activity (and, for that matter, estrogen supplementation) or an augmented sensitivity of target cells to estrogen action appears to increase the risk of cancer of the breast and endometrium.\(^59–65\) Although breast and endometrial cancers would be expected to affect overall longevity by causing premature death in a subset of women, the lasting effect of estrogen would offset the increased risk for cancer by lowering cardiovascular risk.

If menopause and estrogen are determinants of human aging, can they also explain the sexual dimorphism of blood pressure in humans?\(^66^\) Not only are women different than men in age-dependent profiles of blood pressure, but they also exhibit a curious difference from men in that a number of physiological parameters that are correlated with blood pressure in men (eg, cellular ion transport systems and the response of the renal vasculature and the adrenal glands to altered sodium intake) are poorly correlated with blood pressure in women.\(^67–69\) A possible explanation of this gender effect may be that estrogen exerts a vasoactive effect, confounding the relation between physiological parameters and blood pressure, which are readily observed in men. Indeed, estrogen replacement therapy may lower blood pressure in postmenopausal women.\(^70–75\) This effect appears to be prompt and modest and has been attributed to the modified behavior of a host of homeostatic mechanisms, including the renin-angiotensin system.\(^76–78\) However, a vasoactive effect can hardly explain the relation between estrogen and blood pressure with regard to menopause. The postmenopausal period is marked by an abrupt decline in circulating estrogen, whereas the catch-up in systolic blood pressure of postmenopausal women with men can take as long as 20 years.\(^4,79\) A more satisfactory explanation for the effect of estrogen on blood pressure is that estrogen (during the premenopausal period) retards and its absence (during the postmenopausal period) accelerates biologic aging. Such a concept can be tested by monitoring biologic indicators of human aging. It turns out that one of these indicators may be telomere length.

**The Telomere Hypothesis of Cellular Aging**

Telomeres, the TTAGGG repeats at the ends of mammalian chromosomes, impose a limit on cellular replication by undergoing progressive attrition with replication of cultured somatic cells. Telomere length is, hence, a biomarker of the replicative history of these cells. Although the rate of telomere attrition differs among cell types,\(^80\) the ultimate outcome of this process is cessation of replication (ie, replicative senescence), which is often referred to as the Hayflick limit.\(^81,82\) In human somatic cells, this occurs when telomere length becomes critically short. Telomere length varies among chromosomes,\(^83\) but replicative senescence correlates with the mean length of telomeres and not with the length of the shortest telomere.\(^84\) It is important to note in this context that the replicative senescence of cultured somatic cells from rodents is not determined by telomere length.\(^85\)

A reverse transcriptase termed telomerase elongates telomeres through the de novo synthesis of TTAGGG repeats, thereby counteracting telomere attrition.\(^86,87\) Cultured somatic cells from humans exhibit rudimentary or no telomerase activity. In contrast, most cancer cells or immortalized cell
lines show robust telomerase activity and almost limitless replicative capacity. Recent research has proved that the telomere clock serves not only as a biomarker of cellular replication but also as a central determinant of cellular senescence. This was shown by ectopically expressing the catalytic component of telomerase in cultured somatic cells that lack telomerase activity and by inhibiting telomerase in cancer cells. Although the forced expression of telomerase in somatic cells promotes an unabated or a substantially extended replicative capacity in concert with curtailment of telomere attrition, inhibition of telomerase in cancer cells results in rapid telomeric attrition and cell death.

A well-established hypothesis proposes that aging results from cumulative cellular damage over a lifetime and that reactive oxygen species are the main source of this damage. Reactive oxygen species are important determinants in cardiovascular biology and pathobiology and were recently found to increase the rate of telomere attrition per each cycle of cellular replication. Of interest is the fact that homocysteine, a known risk factor for human atherosclerosis, enhances the rate of telomere attrition per replicative cycle in cultured human vascular endothelial cells. To a large extent, this effect appears to be mediated by reactive oxygen species. Based on these experiments, a new factor, namely, telomere attrition, appears to emerge as a link between cardiovascular risk factors and biologic aging of the vasculature in humans.

Overall, empiric and experimental observations of telomere biology fully support the telomere hypothesis of cellular aging, originally proposed by Harley and colleagues. The hypothesis simply posits that telomeres serve as a mitotic clock. The young field of telomere biology, therefore, casts a new perspective on age in vitro, distinguishing biologic age, clock. The young field of telomere biology, therefore, casts a new perspective on age in vitro, distinguishing biologic age, time.

Telomeres and Biologic Aging In Vivo
Telomere attrition is an unlikely determinant of biologic aging in rodents. Within the short life-spans of rodents, telomere erosion does not result in sufficiently short telomeres to modify biologic characteristics or curtail somatic cell growth. A noted exception is the telomerase “knockout” mouse. It takes 6 generations of telomerase-null mice to produce offspring with critically shortened telomeres. Sixth-generation knockout mice are sterile and exhibit a number of features suggestive of accelerated biologic aging. In contrast to rodents, humans exhibit not only the longest life-span among mammals but also relatively short telomeres. O’Brien et al proposed that by curtailing the proliferative potential of somatic cells, telomere attrition is a trait that has evolved to minimize cancer risk in long-lived animals. In humans, the tradeoff for cancer risk may well be a considerable erosion in telomere length during the human life-span, but it is not known at present whether human telomeres are a determinant or only a biomarker of the aging process in vivo.

Several features render human telomeres suitable for the tall task of biologic timekeeping in vivo: (1) telomere length is highly variable among humans; this is observed at birth and thereafter; (2) telomere length is highly heritable; (3) telomere length is inversely related to chronological age; and (4) telomere length is longer in women than in men. The heritability and variability of telomere length among humans are supportive of the role of genetic factors in the biology of human aging. Longer telomere length in women than in men is consistent with the notion that for a given chronological age, women are biologically younger than men, which is in line with the greater longevity of women.

The gender-related difference in telomere length is probably the lasting signature of estrogen, because estrogen stimulates telomerase and an estrogen response element exists on the catalytic subunit of the enzyme. Because estrogen receptors are ubiquitous and present in vascular cells, it is only reasonable to deduce that different cell types are targets of this hormone. It follows then that estrogen-mediated surges in telomerase activity during the menstrual cycle may attenuate telomere attrition rates in multiple tissues including blood vessels. In the vasculature, this “genomic” effect of estrogen should be distinguished from its “nongenomic” effect, which appears to cause vasodilation. Of note, however, is the likelihood that not only estrogen but also other steroid hormones, which are involved in cell growth, affect telomerase activity in vivo. In the final analysis, the balance among these hormones may influence the activity of the enzyme and the rate of telomere attrition at any given time.

Telomere Length and Pulse Pressure in Humans
Given that age-dependent rise in pulse pressure is in large part an indicator of arterial aging and that telomere length may be a molecular record of biologic aging, it was reasonable to examine the relation between telomere length and pulse pressure. A study performed in a relatively small cohort of young adults found that after age adjustment, telomere length was inversely related to pulse pressure. That is, persons with relatively short telomeres were more likely to have a higher pulse pressure. Another study examined the relation between telomere length and pulse pressure in a larger cohort of persons aged 25 to 85 years. In addition, this study assessed aortic stiffness through measurements of aortic pulse wave velocity. The results unraveled a gender effect in the relation between telomere length and pulse pressure as follows: pulse wave velocity was a significant factor that accounted for variation in pulse pressure in men but less so in women. In men, telomere length, but not chronological age, provided an additional explanation of variations in pulse pressure, such that men with shorter telomeres presented with a larger pulse pressure. In women, chronological age, but not telomere length, provided an additional explanation of variation in pulse pressure. Thus, direct indicators of biologic aging, namely, pulse wave velocity and telomere length, gave a better account of variations in pulse pressure among men than among women, an observation attributed to gender-related differences in biologic aging. A tentative conclusion derived from these 2 studies is that the biologic age of persons with relatively wide pulse pressures is more advanced than their chronological age would indicate. This research sug-
gests, therefore, that in a subset of the human population, wide pulse pressure denotes a forward resetting of biologic age.

Conclusions
The recent emphasis on systolic and pulse pressures rather than diastolic blood pressure as major cardiovascular risks represents a departure from a long-held convention and underscores the very fact that in humans, essential hypertension is in large part a disease of aging. The genes that harbor susceptibility to essential hypertension have thus far eluded detection, perhaps because of the complexity of this disorder. However, with the human genome sequence now in hand and with the power of molecular biology and computational genomics, it will be only a matter of time, as was recently suggested,

before the genes that cause essential hypertension are identified. Alternatively, and more likely, the search for genes that cause essential hypertension will not be successful unless the genetic models used in this search account for not only a host of genetic and environmental circumstances unique to modern humans but also the aging factor. That is, the action of hypertensive genes can make sense only in the context of other genes, particularly genes that determine biologic aging.

Herein lies a clear shortcoming of animal research. It is not that the study of animal models with genetic hypertension is unrevealing or less relevant than clinical research. On the contrary, animal research has thrust the field of essential hypertension into previously uncharted territories, generating new and exciting appreciation of hypertension at the cellular and molecular levels. What is in question is the premise that the variant genes that cause hypertension in inbred, short-lived animals also cause essential hypertension in humans. No doubt, variant genes account to a great extent for not only a host of genetic and environmental factors associated with increased pulse pressure among middle-aged men and women is explained by a high systolic blood pressure. J Hypertens. 2000;18:417–423.

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