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Arterial and Cardiac Aging: Major Shareholders in Cardiovascular Disease Enterprises

Part I: Aging Arteries: A “Set Up” for Vascular Disease

Edward G. Lakatta, MD; Daniel Levy, MD

The Demographic Imperative and the Risk of Vascular Diseases in Older Persons

Our population is aging; in the United States today there are 35 million people 65 years of age or older. That number will double by the year 2030 (Figure 1). Although epidemiological studies have discovered that lipid levels, diabetes, sedentary lifestyle, and genetic factors are risk factors for coronary disease, hypertension, congestive heart failure, and stroke, the quintessential cardiovascular diseases within our society, advancing age unequivocally confers the major risk. The incidence and prevalence of these diseases increase steeply with advancing age (Figure 2). Not only does clinically overt cardiovascular disease increase dramatically with aging, but so do subclinical or occult diseases, such as silent coronary atherosclerosis. Figure 3 (top) shows that a substantial percentage of older, community-dwelling, otherwise healthy volunteers have evidence of inducible ischemia during combined thallium/ECG treadmill stress testing, and their prognosis is poor compared with their counterparts without subclinical coronary disease (Figure 3, bottom).

Advancing Age: The Major Risk Factor for Vascular Disease

There are several possible explanations for the dominant effect of age on the likelihood for occurrence of these cardiovascular diseases. One is that aging is synonymous with disease; however, many people achieve “old age” without evidence of these diseases. Another explanation for the “epidemic” of cardiovascular disease in older persons is that other defined risk factors co-vary in number or severity with increasing age. A related, but distinct, idea is that increasing age contributes to an increased exposure time to these other age-dependent risk factors. According to this view, time indirectly confers an increased risk for the occurrence and increased severity and extent of pathophysiological manifestations of these diseases in older persons. A somewhat different view is that cardiovascular structure and function change with time because an “aging process,” and that, over time, this process alters the substrate on which

specific pathophysiological disease mechanisms, such as those that have been linked to experimental atherosclerosis, become superimposed. According to this view, the enhanced risk for older persons to encounter the above diseases is due to age–disease interactions. In other words, age impacts the severity of disease manifestations for a given time at risk. Thus, age-associated changes in cardiovascular structure and function become “partners” with pathophysiological disease mechanisms to determine the threshold, severity, and prognosis of cardiovascular disease occurrence in older persons. Of course, the true interactions are more complex and involve age, multiple risk factors, and genetics. Whereas we have begun to understand some aspects of the former two, the latter most likely involves complex genetic traits that, by and large, remain elusive. With the sequencing of the human genome and the availability of high-throughput genotyping to detect polymorphic allele variation on a population-wide basis, however, breakthroughs may be on the horizon.

To define why age (or an aging process \times exposure time interaction) is so risky with respect to the aforementioned vascular diseases, the specific components of the risk associated with age must be identified. Two complimentary approaches have evolved. On the one hand, epidemiologists are searching for novel measures of “subclinical disease” (in addition to the more established risk factors that have already been well characterized) in large, unselected study cohorts composed of persons both with and without cardiovascular disease. In contrast, gerontologists are attempting to develop quantitative information on cardiovascular structure and function in apparently healthy individuals to define and target the specific characteristics of aging that render it such a major risk factor for cardiovascular disease, even in the absence of clinically apparent comorbidity. The latter approach consists of identifying and selecting community-dwelling individuals who do not have (or have not yet experienced) clinical disease and who do not have occult disease that can be detected by noninvasive methods. These individuals are then grouped by age and stratified according to the level of a given variable, which may include some of the novel measures of subclinical

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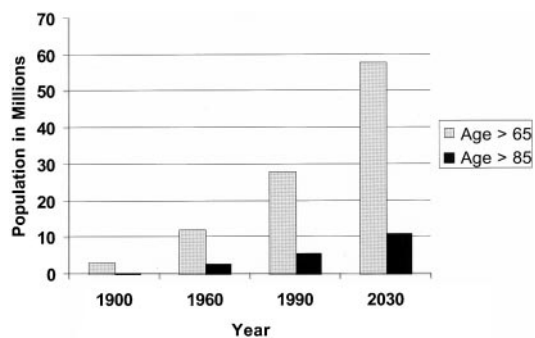


Figure 1. The demographic imperative. Numbers of persons 65 years of age or older (light bars) and 85 years of age or older in the United States from 1900 through 2030. Data taken from the US Census Bureau data with projections for 2030.

disease identified by the epidemiologists. If the variable is perceived as beneficial or deleterious with respect to cardiovascular structure or function, those with extreme measures are considered to be aging “successfully” or “unsuccessfully,” respectively. “Unsuccessful” aging in this context is not synonymous with having clinical disease, as individuals with defined overt or occult clinical disease have been excluded from consideration a priori. Instead, unsuccessful aging, ie, falling within the poorest category with respect to the measure viewed as deleterious, may be viewed as a risk factor for future clinical cardiovascular disease. In this regard, unsuccessful aging is a manifestation of the interaction of the vascular aging process and specific aspects of vascular disease pathophysiology. Thus, gerontologists and epidemiologists have become part of a joint effort in the quest to define why aging confers enormous risk for cardiovascular disease.

The central thesis of this review is that quintessential clinical cardiovascular diseases of older persons and age-associated changes in cardiovascular structure and function, heretofore not defined as disease, become intertwined and interdependent. The role of specific age-associated changes in cardiovascular structure and function in this age–disease interaction has formerly been, and largely continues to be, unrecognized by those who shape medical policy. Thus, specific aspects of cardiovascular aging have remained outside the bailiwick of clinical cardiology, and, until recently, have not been considered in most epidemiological studies of cardiovascular disease. Our main goal is to promote a new research frontier by defining our current understanding of the age-associated changes in cardiac and vascular structure and function that occur in apparently healthy persons and how these are related to the risk of subsequent cardiovascular disease occurrence. This goal is pursued in this and the additional two articles of this series that will occur in subsequent issues of *Circulation*^{1,2} to provoke thought regarding the new and important research efforts to design basic experiments that elucidate these mechanisms and clinical trials that evaluate strategies aimed at reducing or preventing those aspects of aging, such as age-associated increases in large vessel lumen, wall thickening, and stiffness, that occur in apparently healthy persons but confer risk for overt clinical cardiovascular disease.

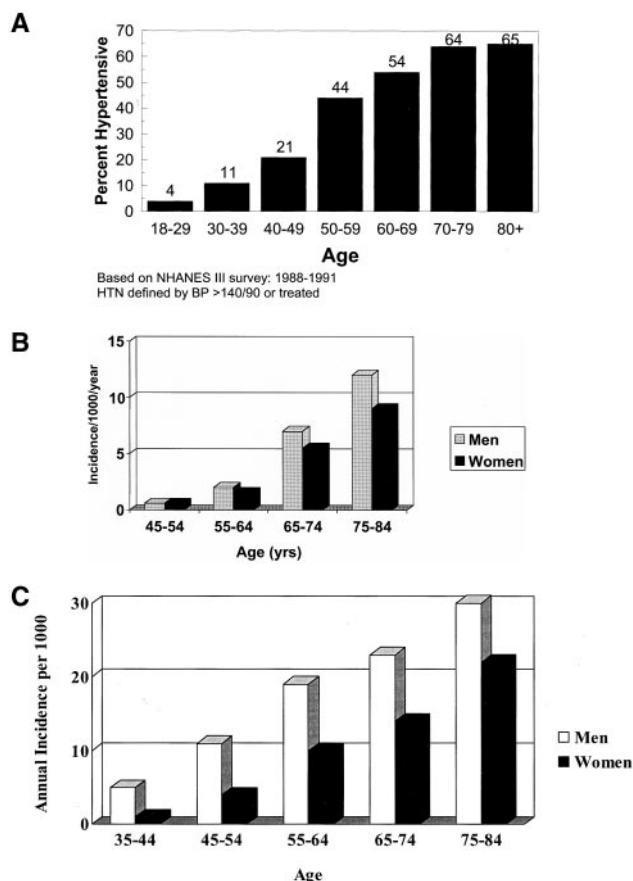


Figure 2. A, Prevalence of hypertension, defined as systolic blood pressure ≥ 140 , diastolic blood pressure ≥ 90 , or current use of medication for purposes of treating high blood pressure. Data are based on National Health and Nutrition Examination Survey III (1988–1991) (Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension*. 1995;25:305–313). B, Incidence of atherothrombotic stroke (per 1000 subjects per year) by age in men (light bars) and women (dark bars) from the Framingham Heart Study. Data from Wolf PA, Lewis A. Conner lecture: contributions of epidemiology to the prevention of stroke. *Circulation*. 1993;88:2471–24783. C, Incidence of coronary heart disease by age in men (light bars) and women (dark bars) from the Framingham Heart Study. Data from Kannel WB, Wolf PA, Garrison RJ, eds. *Framingham Study: An Epidemiological Investigation of Cardiovascular Disease*. Section 34. NIH Publication No.87–2703. Bethesda, Md: National Heart, Lung and Blood Institute; 1987.

Age-Associated Changes in Vascular Structure and Function in Apparent Health

During the past 2 decades, a sustained effort has been ongoing to characterize the effects of aging on multiple aspects of cardiovascular structure and function in a single study population in the Baltimore Longitudinal Study on Aging (BLSA).³ These community-dwelling volunteers are rigorously screened to detect both clinical and occult cardiovascular disease and are characterized with respect to lifestyle (eg, diet and exercise habits) in an attempt to identify and clarify the interactions of these factors and those changes that result from aging.³ Perspectives gleaned from these studies, as well as relevant information regarding cardiovascular

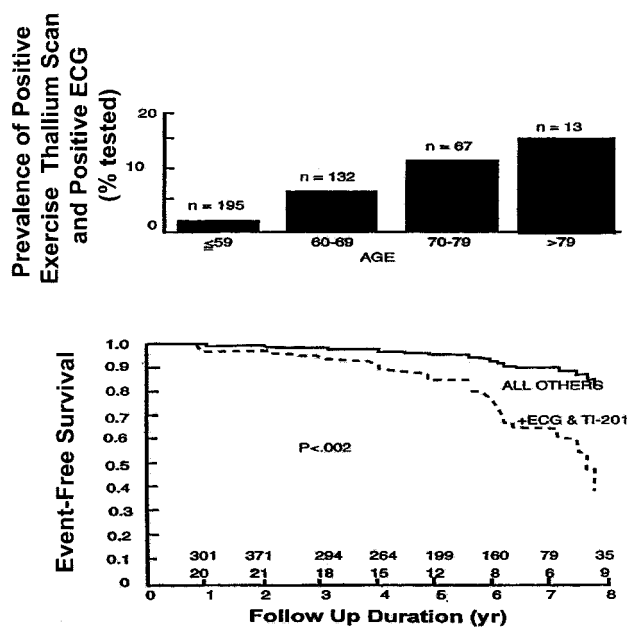


Figure 3. Top, The prevalence of silent ischemia in apparently healthy asymptomatic BLSA volunteer subjects. Silent ischemia is defined as both a positive thallium scan (TI-201) and a positive ECG during maximal exercise. N indicates the number of test performed. From Fleg JL, Gerstenblith G, Zonderman AB, et al. Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers *Circulation* 1990;81:428-436, and Fleg JL, et al, Gerontology Research Center, National Institute on Aging, Baltimore, Md, unpublished data. Bottom, The event free survival rates in those with a double positive (ECG + TI-201) is markedly reduced compared with all other volunteers tested. Within 5 years, 50% of those with a double-positive test for silent ischemia developed their initial clinical manifestation of coronary artery disease. Numbers in the lower part of the figure represent the number of subjects monitored during the follow-up period; lower numbers indicate all double positive test; top numbers, all others. Reprinted from Fleg JL, Gerstenblith G, Zonderman AB, et al. Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers *Circulation* 1990;81:428-436.

aging from other studies in humans and in animal models, are revisited here in the context of the findings of large epidemiological studies that have sought to define risk factors for cardiovascular disease morbidity and mortality.

Age-Associated Changes Central Arterial Structure of Humans

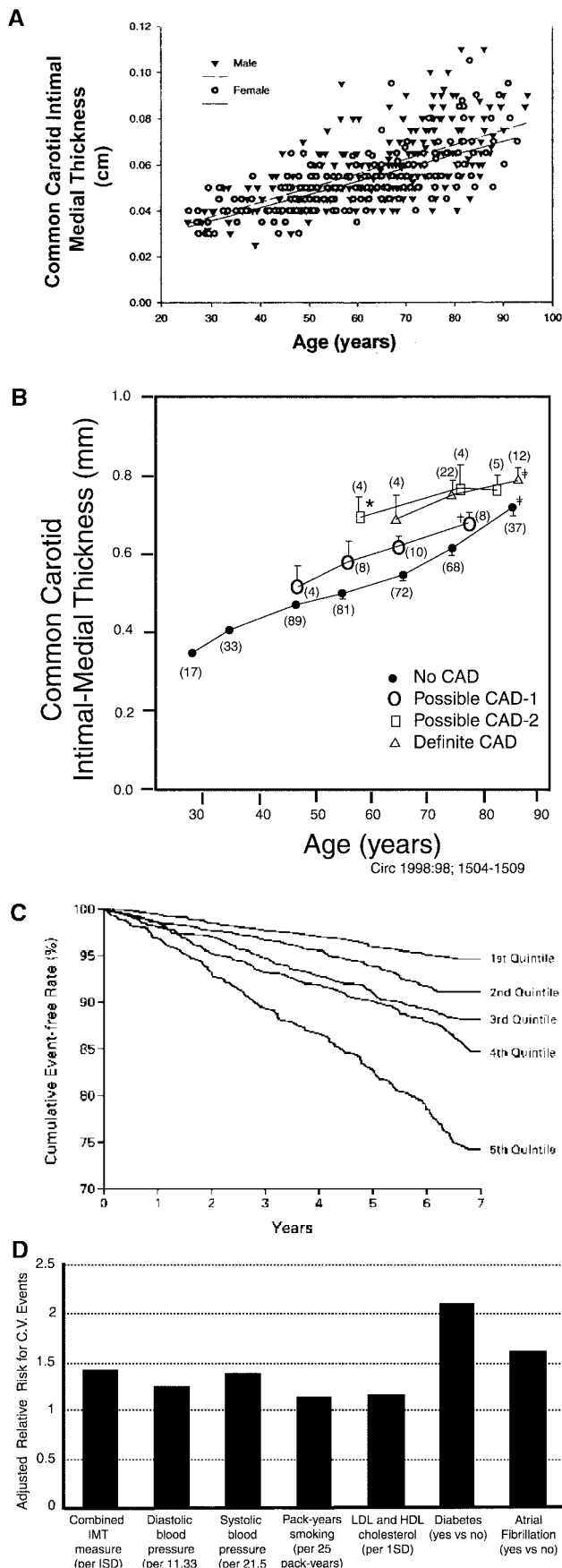
Age-associated changes in the arterial properties of individuals who are considered otherwise healthy may have relevance to the steep age-dependent increase in vascular diseases (Figure 4 and Figure 5). Cross-sectional studies in humans have found that wall thickening and dilatation are prominent structural changes that occur within large elastic arteries during aging.⁴ Postmortem studies indicate that the aortic wall thickening that occurs with aging consists mainly of intimal thickening, even in populations with a low incidence of atherosclerosis.⁵ Noninvasive measurements made within the context of several epidemiological studies indicate

that the carotid wall intimal media (IM) thickness increases 2- to 3-fold between 20 and 90 years of age, which also is the case in BLSA individuals rigorously screened to exclude carotid or coronary arterial stenosis (Figure 4A). Note, however, the marked heterogeneity in IM thickness among individuals of a given age. Although arterial remodeling with aging in otherwise healthy humans occurs in the context of age-associated endothelial dysfunction,⁶ there is presently no detailed information regarding the factors involved in progressive IM thickening with aging in humans.

Increased Intimal Thickening as a Risk Factor for Atherosclerosis

It has been argued that the age-associated increase in IM thickness in humans represents an early stage of atherosclerosis. Indeed, excessive IM thickening at a given age predicts the co-existence of silent coronary artery disease (CAD) (Figure 4B). Because silent CAD often progresses to overt clinical CAD, it is not surprising that increased IM thickness predicts future clinical cardiovascular disease events. A plethora of other epidemiological studies of individuals who were not initially screened to exclude the presence of occult cardiovascular disease have indicated that increased IM thickness is an independent predictor of future cardiovascular events. Note in Figure 4C that the degree of risk varies with degree of vascular thickening, and that the risk gradation among quintiles of IM thickening is non-linear, with the greatest risk occurring in the upper quintile. Thus, older persons in the upper quintile of IM thickness may be considered to have aged unsuccessfully or to have "subclinical" vascular disease. The potency of IM thickness as a risk factor in other individuals equals or exceeds that of most other, more "traditional" risk factors (Figure 4D). Note, however, in Figure 4B that the difference between older and younger persons without evidence of coronary disease far exceeds the difference between older persons free of coronary disease and those with disease. Similar IM thickening occurs with aging in non-human primates and rodents in the absence of atherosclerosis,² and age-dependent IM thickening has also been documented in humans in the absence of atherosclerosis.⁵

The subclinical disease of excessive IM thickening is not necessarily early atherosclerosis. Rather, subclinical IM thickening is strongly correlated with intrinsic arterial aging. Viewed in this way, the increase in IM thickness with aging is analogous to intimal hyperplasia in aortocoronary saphenous vein grafts that serves as the foundation for the later development of atherosclerosis.⁷ Age-associated endothelial dysfunction, arterial stiffening, and arterial pulse pressure widening can also be considered similarly (see below). Combinations of these processes occurring to varying degrees determine the overall vascular aging profile of a given individual. Worse combinations may lead to the most unsuccessful aging within a vessel wall. In humans in Western society, additional risk factors, including hypertension, smoking, dyslipidemia, diabetes, diet, and heretofore unidentified genetic factors, interact with vascular aging (as described above) to activate an atherosclerotic plaque. According to this view, atherosclerosis, which increases with aging, is not a



specific disease but rather an interaction of atherosclerotic plaque with intrinsic features related to vascular aging modulated by atherosclerotic risk factors. Evidence in support of this view comes from studies in which an atherogenic diet resulting in the same elevation of plasma lipids caused markedly more severe atherosclerotic lesions in older versus younger rabbits and non-human primates.^{8,9} Hence, it is possible that atherosclerosis occurring at younger ages may be attributable not only to exaggerated traditional risk factors, but also to accelerated aging of the vascular wall. Of course, the traditional risk factors may themselves accelerate aging of the vascular wall.

Studies in various populations with clinically defined vascular disease have demonstrated that pharmacological interventions, with or without lifestyle (diet, physical activity) interventions, can retard the progression of IM thickening.¹⁰⁻¹⁴ There have been no such studies in persons at high risk for cardiovascular events solely due to unsuccessful vascular aging.

Increased Arterial Stiffening

Age-associated increase in IM thickening is accompanied by both luminal dilatation and a reduction in compliance or distensibility, with an increase in vessel stiffness.² Pulse wave velocity (PWV), a relatively convenient, noninvasive index of vascular stiffening, increases with age both in men and women (Figure 5A). PWV is determined in part by the intrinsic stress/strain relationship (stiffness) of the vascular wall and by the mean arterial pressure. Increased PWV has traditionally been linked to structural alterations in the vascular media, including increased collagen, reduced elastin content, elastin fractures, and calcification. Prominent age-associated increases in PWV have been demonstrated in populations with little or no atherosclerosis, indicating that vascular stiffening can occur independently of atherosclerosis.¹⁵ However, more recent data emerging from epidemiological studies indicate that increased large vessel stiffening also occurs in the context of atherosclerosis and diabetes.^{16,17} The link may be that stiffness is governed not only by the structural changes within the matrix, as noted above, but also by endothelial regulation of vascular smooth muscle tone and of other aspects of vascular wall structure/function. Abnor-

Figure 4. A, The common carotid intimal medial thickness in healthy BLSA volunteers as a function of age. B, Common carotid intimal medial thickness as a function of age, stratified by coronary artery disease (CAD) classification. CAD 2 indicates that group in Figure 3 with double positive tests (see Figure 3 legend). Data for A is from Nagai Y, Metter J, Earley CJ, et al. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. *Circulation* 1998;98:1504-1509. B is reprinted from that same article. C, Common carotid intimal medial thickness predicts future cardiovascular events in Cardiovascular Health Study (CHS). D, Comparison of the associations of age- and sex-adjusted risk factors with the combined event of stroke or myocardial infarction in Cox proportional-hazards models in the CHS study. Note that intimal medial thickness is a potent risk factor for future cardiovascular events. Both C and D reprinted from O’Leary DH, Polack JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340:14-22.

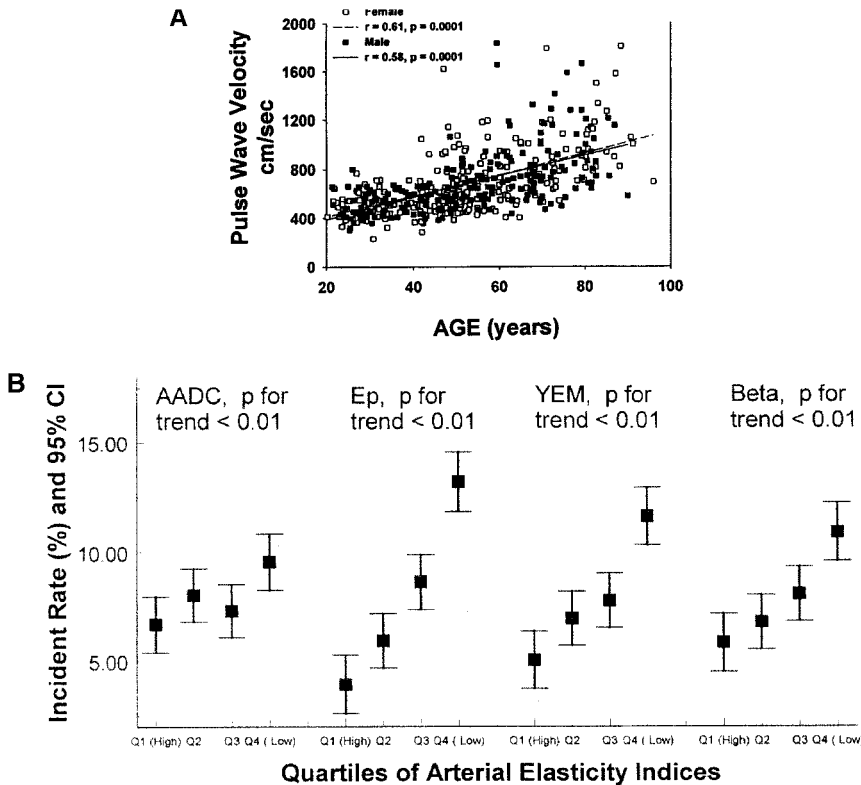


Figure 5. A, Aortic pulse wave velocity as a function of age in healthy BLSA volunteer subjects. From Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation* 1993;88:1456–1462. B, Reduced arterial elasticity in normotensive persons, independent of blood pressure, predicts the future development of hypertension. AADC, EP, YEM, and B are indices of elasticity as defined in sources. Reprinted from Liao D, Arnett DK, Tyroler HA, et al. Arterial stiffness and the development of hypertension: the ARIC Study. *Hypertension* 1999;34:201–206.

malities of the endothelium have been identified to occur early on in the pathophysiology of atherosclerosis, diabetes, and hypertension.¹⁸ Thus, there is evidence of a vicious cycle: altered mechanical properties of the vessel wall influence the development of atherosclerosis and the latter, via endothelial cell dysfunction and other mechanisms, influences vascular stiffness.

As the walls of large arteries become stiffer, central systolic arterial pressure increases, diastolic arterial pressure decreases, and the pulse pressure increases for a given pattern of left ventricular ejection. A longitudinal study of a large population of relatively aged subjects has shown that elevated levels of pulse pressure are associated with progression of IM thickening and that IM thickening, in turn, is associated with widening of pulse pressure.¹⁹ Numerous additional recent studies have concurred that elevated pulse pressure is an independent risk factor for future cardiovascular events.^{16–30} Thus, an increased PWV reflects 3 potential risk factors: increased systolic pressure, widened pulse pressure, and altered vascular wall properties. Recent studies^{17,31–33} indicate that elevated pulse wave velocity and reduced total systemic compliance assessed by stroke volume/pulse pressure, over and above blood pressure, are independent predictors of cardiovascular events. This suggests that altered structure/function of the stiff vessel wall, in addition to the associated increase in systolic and pulse pressures, is a risk factor for future vascular events. It has been hypothesized that cross-links, due to nonenzymatic glycation, that increase with age and increase markedly in diabetes contribute to age- and disease-related increases in large artery stiffening. In this regard, a novel drug that breaks such cross-links has been

shown to reduce indices of arterial stiffness measures in rodents, dogs, non-human primates, and humans.^{34–37}

In fact, recent studies have demonstrated that increased vascular stiffness precedes the development of hypertension (Figure 5B). This concept has been overshadowed by the idea that an increase in mean arterial pressure or peripheral resistance is the predominant cause of increased large artery stiffness. In other words, while the “secondary” increase in large artery stiffness is attributable to an increase in mean pressure that occurs in hypertension, evidence now exists that the “primary” increase in large artery stiffness that accompanies aging gives rise to an increase in large vessel stiffness that precedes an elevation of arterial pressure. Figure 5B illustrates this point. Normotensive individuals who fall within the upper quintiles for measures of arterial stiffness are more likely to develop hypertension (Figure 5B). Observations such as this give rise to the notion that hypertension is in part a disease of the arterial wall. There are compensatory mechanisms to normalize blood pressure that fail with advancing age. For example, endothelial function becomes apparently altered at about the 6th decade (Figure 6A), a time when pulse pressure begins to appreciably elevate (Figure 6B). Thus, the altered endothelial function that occurs with aging may be a mechanism that not only permits arterial pulse pressure to rise but that also underlies the importance of pulse pressure as a risk factor for cardiovascular events, even when systolic pressure is accounted for.

Arterial Pressure

As our definition of disease continues to evolve, we may find that many subjects who were formerly thought to be healthy are not. For example, systolic pressure ≥ 140 mm Hg is now

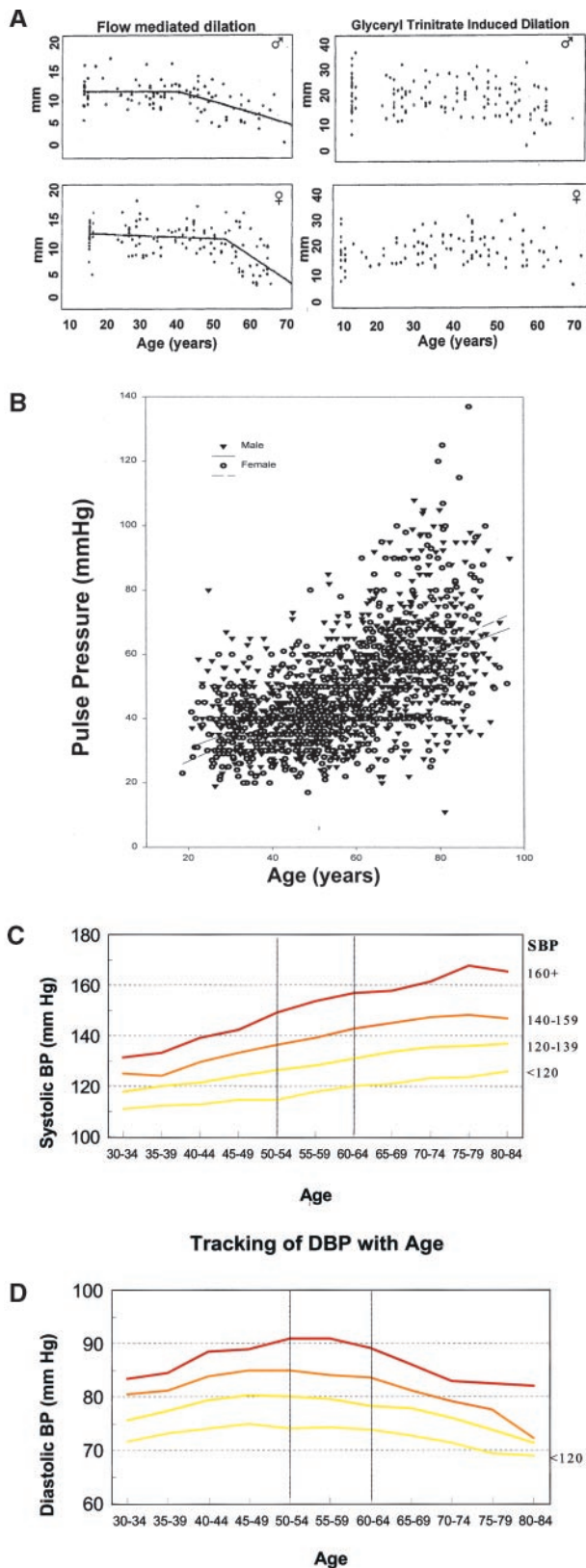


Figure 6. A, Endothelial (flow) mediated and non-endothelial (glyceryl trinitrate) induced arterial dilatation in apparently healthy persons. Note that the marked age-associated decline occurs about a decade later in females versus males. Reprinted from Celermajer DS, Sorensen KE, Spiegelhalter DJ, et al. Aging is associated with endothelial dysfunction in healthy men years

considered to be hypertension, and hypertension is considered to be a disease. Individuals with a systolic pressure between 140 and 160 mm Hg, who a decade ago were thought to be free from disease, are now identified as being diseased. Larger studies have shown that individuals who manifest modest elevations in systolic and pulse pressures are more likely to develop clinical disease or die from it.³⁸

In addition to stroke volume, arterial pressure is determined by the interplay of peripheral resistance and central artery stiffness; the former raises both systolic and diastolic pressure to a similar degree, whereas the latter raises systolic but lowers diastolic pressure. Pulse pressure is a useful hemodynamic indicator of conduit artery vascular stiffness. Framingham investigators and others have reported an age-dependent rise in average systolic blood pressure across all adult age groups (Figure 6C). In contrast, average diastolic pressure was found to rise until 50 years of age, level off from ages 50 to 60, and decline thereafter (Figure 6D). The age-dependent changes in systolic, diastolic, and pulse pressure are consistent with the notion that in younger people, blood pressure is determined largely by peripheral vascular resistance, whereas in older individuals, it is determined to a greater extent by central conduit vessel stiffness.

Owing to the decline in diastolic pressure in older men and women in whom systolic pressure is increasing, isolated systolic hypertension emerges as the most common form of hypertension in individuals over the age of 50.³⁸ Isolated systolic hypertension, even when mild in severity (stage 1), is associated with an appreciable increase in cardiovascular disease risk.^{21,22} Based on long-term follow up of middle-aged and older subjects, however, Framingham researchers have found pulse pressure to be a better predictor of coronary disease risk than the systolic or diastolic pressure.²³ When considered jointly with the systolic blood pressure in older subjects, diastolic blood pressure is inversely related to coronary risk. Consideration of the systolic and diastolic pressures jointly may be preferable to consideration of either value alone.^{21,23,39}

An emerging concept in the treatment of hypertension recognizes that progressive vascular damage can continue to occur even when arterial pressure is controlled. It is conceivable that drugs that retard or reverse age-associated vascular wall remodeling and increased stiffness will be preferable to those that lower pressure without affecting the vascular wall properties.

before the age-related decline in women. *J Am Coll Cardiol* 1994;24:471-476. B, Pulse pressure in healthy BLSA individuals. Reprinted from Pearson JD, Morrell CH, Brant LJ, et al. Age-associated changes in blood pressure in a longitudinal study of healthy men and women. *J Gerontol Med Sci.* 1997;52:M177-M183. C, Tracking of systolic blood pressure with age in Framingham Heart Study subjects. Subjects were stratified in 4 groups according to their systolic blood pressure (SBP) in middle age: <120 mm Hg, 120 to 139 mm Hg, 140 to 159 mm Hg, and ≥160 mm Hg. D, Tracking of diastolic blood pressure (DBP) with age in Framingham Heart Study subjects (same grouping were used as in C). Both C and D adapted from Franklin SS, Gustin W IV, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation* 1997;96:308-315.

Relationship of Vascular Human Aging in Health to Vascular Diseases

Age-Associated Changes	Plausible Mechanisms	Possible Relation to Human Disease
Vascular structural remodeling		
↑ Vascular intimal thickness	↑ Migration of and Ý matrix production by VSMC Possible derivation of intimal cells from other sources	Promotes development of atherosclerosis
↑ Vascular stiffness	Elastin fragmentation ↑ Elastase activity ↑ Collagen production by VSMC and ↑ Cross linking of collagen Altered growth factor regulation/tissue repair mechanisms	Systolic hypertension Left ventricular wall thickening Stroke Atherosclerosis Left ventricular hypertrophy
Vascular functional changes		
Altered regulation of vascular tone	↓ NO production/effects	Vascular stiffening; hypertension Early atherosclerosis
Reduced physical activity	Learned lifestyle Frailty	Exaggerated age changes in some aspects of vascular structure and function, eg, arterial stiffening Negative impact on atherosclerotic vascular disease, hypertension and heart failure

VSMC indicates vascular smooth muscle cell.

Summary

There is a growing body of evidence that increased large artery thickening and stiffness and endothelial dysfunction in apparently otherwise healthy older persons, along with the ensuing increase in systolic and pulse pressure that was formerly thought to be part of “normal” aging, precede clinical disease and predict a higher risk for developing clinical atherosclerosis, hypertension, and stroke (Table). Some of these vascular changes that occur with aging in normotensive humans, including endothelial dysfunction, have been observed in hypertensive patients at an earlier age and are more marked than in normotensive subjects. Such otherwise asymptomatic individuals might be considered to manifest unsuccessful vascular aging. When stated in this context, unsuccessful vascular aging becomes the risk factor for eventual clinical disease manifestations. Some epidemiologists will perceive the risk of unsuccessful vascular aging as synonymous with subclinical cardiovascular disease; however, evidence is mounting that subclinical vascular disease in older persons represents specific aspects of vascular aging and is not synonymous with low-grade atherosclerosis or hypertension. Rather, vascular aging and vascular disease are partners; each contributes specific components to what is presently referred to as “vascular disease.” Thus, what clinical medicine and epidemiology now refer to as vascular disease should be regarded as the “vascular aging–vascular disease interaction.” Aging blood vessels provide the milieu in which vascular diseases can flourish. If vascular aging is a risk factor for disease, then age-associated vascular changes represent a potential target for treatment and prevention. The vascular changes due to aging in persons who do not have a diagnosis of clinical cardiovascular disease have remained largely outside the bailiwick of clinical cardiology, however, and until recently have not been the focus of preventive measures.

Lifestyle intervention or pharmacotherapy to retard the rate of progression of subclinical disease might be considered before the clinical disease becomes manifest. With respect to lifestyle, the risk factor of lack of vigorous exercise increases dramatically with age in otherwise healthy persons.⁴⁰ It is noteworthy that pulse pressure, PWV, and carotid augmentation index are lower^{41,42} and baroreceptor reflex function is improved⁴³ in older persons who are physically conditioned compared with sedentary persons. Exercise conditioning also improves endothelial function in older persons.⁴⁴ In addition, there is evidence to indicate that diets low in sodium are associated with reduced arterial stiffening with aging.⁴⁵ With respect to pharmacotherapy, angiotensin-converting enzyme inhibitors have been shown to retard vascular aging in rodents.^{46,47} Retardation or reduction in IM thickness in humans has been achieved by drug/diet intervention.^{25–29} It is thus far unproved if such treatment can “prevent” unsuccessful aging of the vasculature in individuals of younger-middle age who exhibit excessive subclinical evidence of unsuccessful aging.

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