CHAPTER

6

Cardiovascular Aging: Perspectives from the Baltimore Longitudinal Study of Aging (BLSA)

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INTRODUCTION

The Baltimore Longitudinal Study of Aging (BLSA), a part of the National Institute on Aging (NIA), Intramural Research Program, is America's longest running longitudinal study of human aging, begun in 1958 with approximately 3,200 total volunteers over the life of the study [1]. Participants enter the BLSA at different ages ranging from 20 to 94+ years. Today, more than 1,400 men and women are current study participants who undergo a battery of tests over the course of 3 days and return for repeated tests according to an age-based schedule. CV studies within the BLSA are conducted by the Laboratory of Cardiovascular Science (LCS) of the NIA, Intramural Research Program.

BLSA approach to defining CV Aging (Figure 6.1) begins with an attempt to separate aging and occult and clinical CV disease to the extent to which this is possible in a community dwelling, volunteer cohort.

Apparently healthy individuals over 40 years of age are rigorously screened with thallium scintigraphy and ECG monitoring at maximum effort to detect occult coronary artery disease (CAD). This process identifies apparently 30% of individuals over 70 years of age who have occult coronary disease. Subsequent data on these individuals, and those with overt clinical heart disease of any type, for example, hypertension or CAD, are collected and analyzed with respect to studies of age–disease interactions but not with respect to healthy aging, *per se*. The remaining persons, free from clinical and occult CV disease, are categorized as sedentary or physically active at varying degrees, and resting CV structure and function and functional reserve capacity are characterized with respect to age and lifestyle (physical activity).

Initial characterization of age-associated changes in the CV system utilizes a cross-sectional approach to describe changes over a broad age range. When possible, additional studies are designed, using more sophisticated methodology or acute physiological or pharmacological perturbations, to probe the mechanism of the aging changes described earlier. In some projects, cross-sectional measurements continue to be made to (i) provide greater statistical power to answer certain questions; (ii) address new hypotheses requiring simultaneous measurement of related new variables; (iii) incorporate rapid technological advances requiring *de novo* measurements; and (iv) monitor secular changes in important variables, mediated by lifestyle or environmental changes.

The BLSA is quite unique in that it is a longitudinal study. Longitudinal measurements for many variables are made at pre-defined intervals to identify "true" aging changes, free from the selective survivorship effect of cross-sectional studies. Longitudinal studies make it possible to determine the rate of aging for specific variables in an individual over time. This allows personalization of results due to knowledge of specific events in a participant's lifetime that may lead to particular results. It is helpful in studying the effect of events that occur at different chronological ages in different subjects. Although it is theoretically appealing to perform longitudinal follow-up on all cross-sectional studies, slow rates of change with age, poor test reproducibility, and rapid

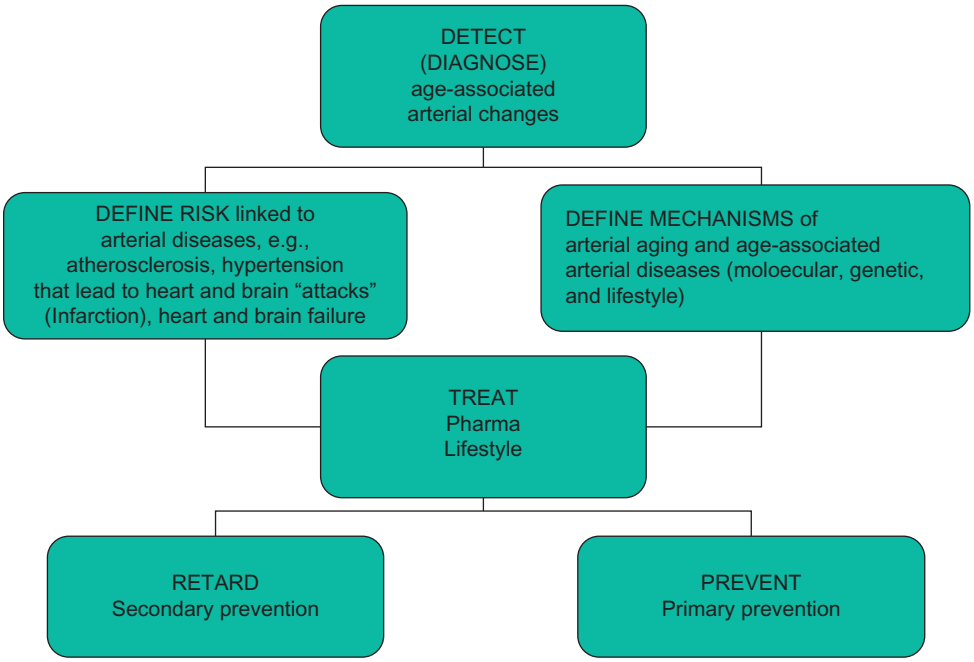

FIGURE 6.1 BLSA research goals.

technological advances, often weaken the value of such longitudinal efforts. Another type of longitudinal study may monitor "outcomes" or "events" in relation to an initial measurement variable, such as myocardial infarction (MI) or cardiac death as predicted by prior exercise ECG and thallium scanning.

BLSA cross-sectional and longitudinal studies frequently generate hypotheses that can only be tested by intervention studies. Although chronic or long-term interventions are not generally made in BLSA volunteers to avoid bias in future measurements, short-term interventions, however, such as physiological or pharmacological perturbations are typical of hypothesis-driven studies often used to define the mechanisms of aging changes observed in cross-sectional or longitudinal studies. We have recruited outside populations, as needed, to address such interventions, using the BLSA panel as a control group. Counterparts of important age-associated phenotypic changes identified in BLSA humans are identified in animal models, in which cellular and molecular mechanisms can be investigated (Figure 6.1). Discoveries made at this level are referred back to studies in intact animals for proof of concept intervention studied. In selective instances this is followed by demonstration trials in human, and when successful, translated into multicenter clinical trials (Figure 6.1). This approach has resulted in the discovery and translation to clinical utilization, an example of which are paclitaxel-coated stents in the context of acute arterial damage [2].

LCS has maintained a primary focus on arterial stiffening and cardiac reserve in its BLSA studies in humans and explored the various facets of aging through this lens. Major areas of LCS research in the BLSA have included the following.

1. Age-associated changes in cardiac structure, resting ventricular function, rhythm, and conduction.
2. Effects of age, gender, and lifestyle variables on aerobic capacity and hemodynamic neurohormonal reserve responses to acute stress.
3. Age-associated changes in arterial structure and function and their effects on cardiac structure and function.
4. Interactions of aging and cardiac disease, with a primary focus on the impact of age-associated CV changes as risk factors for CV disease.

Pursuit of these topics permits detection of accelerated aging in some individuals akin to Early Vascular Aging or Unsuccessful Vascular Aging [3]. A number of corollary discoveries also have been made, which reveal a complex interplay between heart and arterial aging and links between CV aging and CV disease. The present overview of BLSA studies focuses on age-associated changes in arterial structure and function, how these affect cardiac structure/function, and how these age-associated changes affect the "health span of older persons," that is, how these are linked to chronic age-associated CV diseases in older persons. CV research tools utilized in the BLSA are listed in Table 6.1.

TABLE 6.1 BLSA Database Employed in Cardiovascular Studies +, ++

Medical history and physical examination
Plasma samples, metabolic markers, cytokines, sex and adrenal hormones, advanced glycation end products
Resting EKG
Treadmill EKG
Treadmill O_2 consumption
Multiple gated acquisition scans (noninvasive measurement of heart volume throughout each cardiac cycle during upright seated rest and graded exercise cycle ergonometer workloads)
Heart rate and O_2 consumption during cycle ergometry
Myocardial thallium scintigraphy at rest and during maximum exercise
Common carotid artery diameter
Common carotid intimal–medial thickness
Carotid pulse pressure augmentation index
Carotid–femoral pulse wave velocity
Cardiac and arterial magnetic resonance imaging
Cardiac and aortic ultrasound
24 h Holter monitor HR
Electron beam computed tomography (arterial calcification)
Dual X-ray absorptiometry scan

+ Not all tests are made on every visit.
++ Not all tests are made on all subjects.

DETECTING OCCULT CV DISEASE IN BLSA PARTICIPANTS

Community-dwelling BLSA volunteers are rigorously screened to detect both clinical and occult CV disease and are characterized with respect to lifestyle (e.g., diet and exercise habits) in an attempt to identify and clarify the interactions of these factors and those changes that result from aging, *per se*. Often, diagnoses of chronic CV diseases have clinical utility and significance in improving patient outcomes. Asymptomatic CAD is prevalent in the general population, and individuals with CAD are at a greater risk than those who are disease free to progress to symptomatic CAD and cardiac death.

Longitudinal changes in exercise EKG ST segments determined whether the conversion from a normal to an abnormal ST segment response might identify individuals at high risk for a future coronary event.

An abnormal ST segment response to treadmill exercise was ascertained to have a low predictive value for future coronary events (angina pectoris, nonfatal MI, or cardiac death) in apparently healthy individuals indicated by analysis of serial exercise tests performed at 2–4-year intervals in 726 apparently healthy male and female volunteers, aged 22–84 years (mean, 55.1 years), from the BLSA12-lead electrocardiogram [4]. Over a mean overall follow-up of 7.4 years, coronary events occurred in 19.1% of those with an abnormal ST response to exercise versus 5.5% in those with a normal response. After adjustment for standard coronary risk factor, among individuals with an abnormal ST segment response, by proportional hazards regression analysis, the incidence of events was virtually identical between those with an initially abnormal response (group 1) and those who converted from a normal to an abnormal response (group 2), 19.8% versus 18.5%.

Combined thallium scintigraphy and electrocardiography (ECG) examined whether detection of reduced regional perfusion by thallium scintigraphy improved the predictive value of exercise-induced ST segment depression in BLSA participants.

We performed *both* maximal treadmill exercise ECG and thallium scintigraphy (201Tl) in 407 asymptomatic volunteers [5] to detect the prevalence of exercise-induced silent ischemia (SI), defined by concordant ST segment depression and a thallium perfusion defect. Thus, in this asymptomatic BLSA population, the presence of

exercise-induced silent myocardial ischemia increases progressively with age and identifies a small group of subjects with a strikingly high incidence of subsequent coronary events.

Risk Factors for Silent Myocardial Ischemia

Because it appeared that exercise-induced SI showed promise in accurately predicting future coronary events, we investigated potential risk factors for exercise-induced SI in 281 apparently healthy BLSA volunteers [6] and compared their risk factor profiles with those of 132 patients with overt CAD. SI was defined as concordant exercise-induced asymptomatic ST-segment depression on ECG and perfusion defects on tomographic thallium-201 scintigraphy [6] were detected in 37 of 225 men (16%), versus 2 of 56 women (4%). Older age, male gender, abdominal obesity, and reduced HDL levels—all well-established risk factors for overt CAD—were also risk factors for exercise-induced SI in these asymptomatic BLSA volunteers.

Chest Pain Reports Are Linked to Personality

The direction of the causal connection of chest pain and psychological disorders was investigated in a longitudinal retrospective-predictive study of CAD diagnoses in a sample of 123 men followed for periods of up to 20 years [7]. Neuroticism scores (N) were not significantly related to CAD but were significantly correlated with 13 of the 48 chest pain variables. In addition to correlating positively with the chest pain variables that were negatively correlated with CAD, N scores were significantly related to higher pain severity ratings, being angry, annoyed, tense, afraid, worried, distress before the chest pain, breathlessness during the pain episode, stabbing pain. Thus, recognition of patients' characteristic levels of distress or neuroticism discovered in BLSA analysis may aid physicians in evaluating symptoms more accurately and in treating their chest pains more appropriately.

In a follow up study in cardiology patients at Johns Hopkins Hospital [8] the relations among self-reported and physician-estimated chest pain variables to angiographically determined coronary artery disease (CAD) and N scores. That N influences chest pain reports more than actual stenosis is further confirmed by the results of physicians' ratings of their patients' typical chest pain episodes. Thus, recognition of patients' characteristic levels of distress or neuroticism discovered in BLSA analysis may aid physicians in evaluating symptoms more accurately and in treating their chest pains more appropriately.

EPIDEMIOLOGICAL STUDIES OF GENETIC AND HORMONAL AND METABOLIC RISK FACTORS FOR CAD

LCS has conducted a variety of studies in the BLSA examining how factors such as diet, exercise, gender, genetics, and hormonal changes interact with age to impact CV health. Such studies are important, as there is always much discussion of what is "good" for one's CV health and all too often baseless conjectures are made. These studies provide more concrete evidence for modifying lifestyle and behaviors to positive effects.

Metabolic Risk Factors

The longevity of different animal species is inversely proportional to their energy expenditure. Animals exposed to restriction of food intake experience a substantial increment in lifespan. This "rate of living" theory, namely that energy production and expenditure are related to longevity and to the aging process, has not been previously tested in humans. The relationship between resting metabolic rate (RMR) and incident metabolic syndrome (MetS) was examined in 353 BLSA subjects who did not have the MetS at baseline, 19% developed the MetS an average follow-up of 16 ± 7 years. In multivariate analyses, RMR indexed to lean body mass was an independent predictor of incident MetS in the BLSA.

To determine the predictors of incidence of MetS (Adult Treatment Panel III criteria) and to determine how longitudinal changes in specific MetS components vary by age or gender, we compared participants who developed MetS versus those who did not [9]. Thus, the patterns of MetS components and the longitudinal changes that lead to the MetS are different in men and women. Men were more likely than women to have the MetS without obesity, whereas women were more likely than men to have the MetS without an altered glucose metabolism.

Interestingly, components with the highest prevalence prior to MetS development, such as elevated blood pressure, are not *necessarily* the stronger risk factors.

ApoE4 and the Longitudinal Changes in CV Risk Factors

There had been several studies published on the association of the presence of the apolipoprotein E4 (ApoE4) allele and the increased risk of CVD in men. The ApoE polymorphism is estimated to explain 4–15% of the variation in LDL cholesterol concentrations. The ApoE4 allele frequency is thought to be increased in populations at high risk for atherosclerotic coronary heart disease, and to be lower in geographic regions where this disease is less prevalent.

Although the ApoE4 genotype has previously been associated with high cholesterol levels, it had not been ascertained whether it is an independent predictor of coronary heart disease. ApoE genotypes were determined in 730 participants in the BLSA (421 men and 309 women, mean [± SD] age of 52 ± 17 years) who were free of preexisting coronary heart disease [10]. The ApoE4 allele was observed in 200 subjects (27%), including 183 heterozygotes and 17 homozygotes. Coronary risk factor profiles were similar in those with and without ApoE4. In a multivariate model, the ApoE4 genotype is a strong independent risk factor for coronary events in men, but not women. The association however does not appear to be mediated by differences in total cholesterol levels.

The effects of ApoE4 on the increased risk of CV disease are not exclusively mediated through higher cholesterol levels because they also exhibit gender specificity [11]. We compared the longitudinal changes in traditional CV risk factors (blood pressure, body mass index (BMI), total and HDL cholesterol, triglycerides, and blood glucose) in BLSA men with and without the ApoE4 allele. Longitudinal changes in these CV risk factors were analyzed by linear mixed-effects models. ApoE4 was independently associated with accelerated changes over time in fasting plasma glucose but there was no change in those without ApoE4 in the sixth age-decade over 10 years. No significant effect of ApoE4 on longitudinal changes in total or HDL cholesterol, triglycerides, or blood pressures was observed. Thus, ApoE4 primarily influences fasting plasma glucose and its changes over time.

Plasma Levels of Estradiol, Testosterone, and Dehydroepiandrosterone-Sulfate

Prior studies had reported men with CAD to have elevated plasma levels of estrogens and reduced concentrations of dehydroepiandrosterone (DHEA) or DHEA-sulfate (DHEAS). Whether gonadal steroids or DHEAS are risk factors for CAD was determined, using a prospective design, in BLSA men studied at regular intervals [12]. Our results indicate that plasma adrenal and gonadal steroids do not strongly influence CAD risk and that cholesterol and systolic blood pressure (SBP) are more important CAD risk factors in young and old men, respectively. Moreover, our findings were consistent with those that indicate a cardioprotective role for endogenous E_2 in men, as well as in women.

AGE-ASSOCIATED CHANGES IN PULSE WAVE VELOCITY (PWV) AND THE ARTERIAL WAVEFORM

While CV aging is without question the product of a complex set of developments in multiple physiologic systems, BLSA has consistently focused on the central role that arterial parameters play in the overall phenotype. By structuring its resources around the question of arterial aging (Figure 6.2). LCS has been able to quickly build on its discoveries from animal/cellular research and apply them to longitudinal studies and clinical trials in human populations as well as directing projects in the opposite direction by exploring our findings from human studies in animal/cellular models. This has enabled many early reports of the associations between aging and dilation of the large arteries, dilation of the aortic root, thickening of the common carotid intimal–medial layer, arterial stiffness, and associations between arterial stiffness (PWV), and a variety of covariates.

A BLSA study published in 1977 was the first of its kind to use the noninvasive echocardiogram (Figure 6.2), setting LCS on the path to examining changes in arterial structure and function in further detail [13]. Echocardiograms were performed on 105 male BLSA participants. All subjects (25–84 years of age) were physically active and had no evidence of hypertension or CV disease. Increasing age correlated with increased aortic

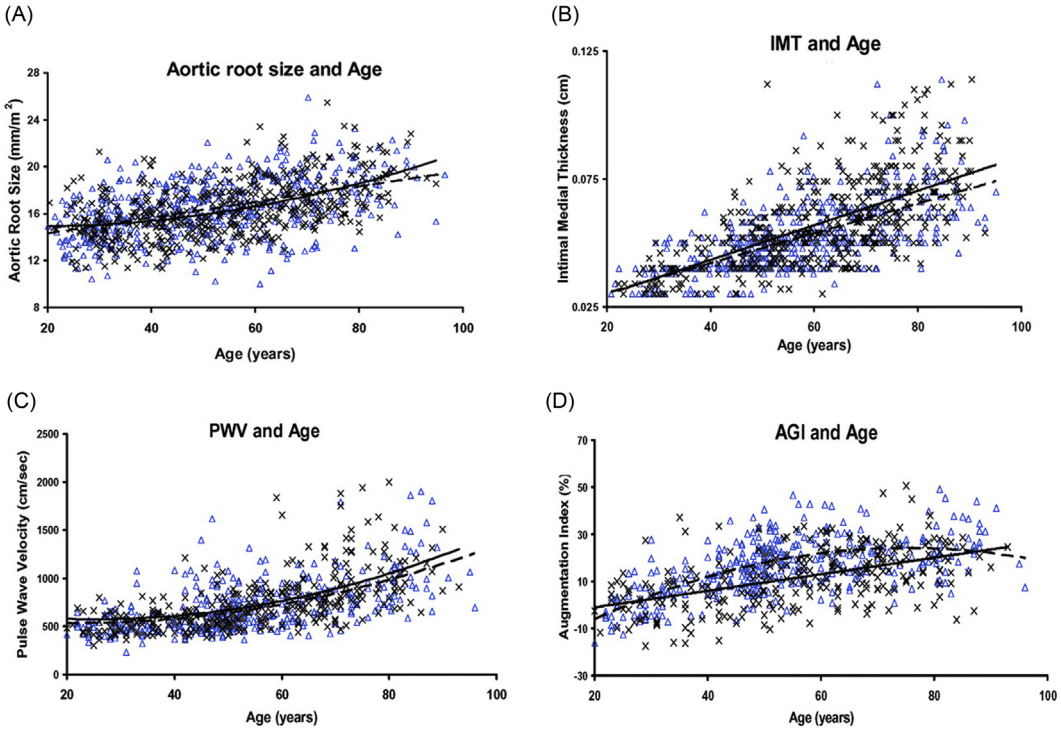

FIGURE 6.2 Age-associated changes in vascular structure and function in men (x) and women (Δ). Best fit regression lines (quadratic or linear) are shown for men (solid lines) and women (dotted lines). (A) Aortic root size, measured via M-mode echocardiography. (B) Common carotid Intimal–Medial Thickness. (C) Carotid–femoral pulse wave velocity (PWV). (D) Carotid arterial augmentation index (AGI), defined as the ratio of the distance from the inflection point to the peak of the arterial waveform, over the pulse pressure. Note that unlike PWV, which increases quadratically with age, the age-associated increase in AGI is linear in men and convex shape in women, suggesting that factors other than stiffness also modulate the origin of reflected waves and the amplitude of AGI.

root diameter and left ventricular (LV) wall thickness (Figure 6.2). Between 1977 and 2013, various studies conducted with the BLSA shed light on the apparently crucial role of changes in arterial structure with age on CV health and function.

Independent Determinants of Aortic Stiffness (PWV) and Central Pressure Augmentation (AGI)

Age, Aerobic Capacity, and Arterial Stiffness

Prior studies had established that arterial stiffness manifests as an increase in arterial PWV or late systolic amplification of the carotid artery pressure pulse, increases with age. However, the populations studied in prior investigations were not rigorously screened to exclude clinical hypertension, occult coronary disease, or diabetes. Furthermore, it is unknown whether exercise capacity or chronic physical endurance training affects the age-associated increase in arterial stiffness. Thus, it became increasingly urgent to conduct a study where such confounding factors for increasing arterial stiffness with age could be further clarified. In order to use arterial stiffness as our benchmark to predict age-associated CV disease, it became important to confirm these studies in rigorously screened patients. Furthermore, if it could be determined that exercise mitigates age-associated arterial stiffness, exercise could be used as a preventive measure against developing CV disease.

Carotid arterial pressure pulse augmentation index (AGI), using applanation tonometry, and aortic pulse wave velocity (APWV) were measured in 146 male and female BLSA volunteers 21–96 years replicated, who were rigorously screened to exclude clinical and occult CV disease [14]. In this healthy, largely sedentary cohort, the arterial stiffness indexes AGI and APWV increased approximately fivefold and twofold, respectively, across the age span in both men and women, despite only a 14% increase in SBP. These age-associated increases in AGI and APWV were of a similar magnitude to those in prior studies of less rigorously screened populations. 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 though abnormal endothelial function, linked to the thickening, may also play a role. Analysis of PWV data has increasingly demonstrated the central role of arterial stiffness in the CV-aging process and encouraged our group to explore aspects of arterial pulse wave and arterial flow mechanics in greater detail.

Aerobic capacity was determined in all individuals by measurement of maximal oxygen consumption (VO_2max) during treadmill exercise. Both AGI and APWV varied inversely with VO_2max, and this relationship, at least for AGI, was independent of age. In endurance trained male athletes, 54−75 years old (mean = 44), the arterial stiffness indexes were significantly reduced relative to their sedentary age peers (AGI, 36% lower; APWV, 26% lower) despite similar blood pressures. Thus, in normotensive, rigorously screened volunteers in whom SBP increased an average of only 14% between ages 20 and 90 years, major age-associated increases of arterial stiffness occur because higher physical conditioning status, indexed by VO_2max, were associated with reduced arterial stiffness, both within this predominantly sedentary population and in endurance trained older men relative to their less active age-matched peers. This suggests that interventions to improve aerobic capacity may mitigate the stiffening of the arterial tree that accompanies normative aging. These findings have high clinical and translational value as exercise and lifestyle changes could be used prevent CV disease. Additional studies on what levels of aerobic activity, types of aerobic activity, etc. could be implemented to determine which types of physical activity are best at reducing age-associated arterial stiffening. Such studies are extremely important as they allow the breadth of research on changes with aging to be applied translationally on a patient level, which is always the ultimate goal.

Inter-Arm Difference in Systolic Blood Pressure

Inter-arm difference in systolic blood pressure (IADSBP) has recently been associated with increased adverse CV outcomes associated with arterial stiffness. Inter-arm difference in blood pressure can be measured quite easily clinically and could become a potent tool in future diagnostics. We hypothesized [15] that part of this association is mediated by arterial stiffness, and examined the relationship between significant IADSBP and carotid−femoral pulse wave velocity (CF-PWV) in a sample from the BLSA. Of 1,045 participants. 50 (4.8%) had an IADSBP $\geq$10 mmHg at baseline, and 629 had completed data from $\geq$2 visits (for a total of 1,704 visits during 8 years). CF-PWV was significantly higher in patients with an IADSBP $\geq$10 mmHg. Compared with others, those with IADSBP $\geq$10 mmHg also had higher BMI, waist circumference (WC), triglycerides, prevalence of diabetes, and lower HDL cholesterol. A significant association with IADSBP $\geq$10 mmHg was observed for CF-PWV in both cross-sectional and longitudinal multivariate analyses. Female sex, Caucasian race, high BMI (plus diabetes and low HDL cholesterol only cross-sectionally) were other independent correlates of IADSBP $\geq$10 mmHg.

PWV as a Predictor of the Longitudinal Increase in SBP and of Incident Hypertension in the BLSA

Although arterial stiffness is believed to underlie, in part, the age-associated changes in SBP, particularly at older ages, few longitudinal studies in humans have examined the relationship between arterial stiffness and blood pressure. We evaluated whether PWV, a non-invasive index of arterial stiffness, is a predictor of the longitudinal changes in SBP and of incident hypertension [16]. PWV was measured at baseline in 449 normotensive or untreated BLSA hypertensive volunteers (age 53 ± 17 years). Repeated measurements of blood pressure were performed during an average follow-up of 4.9 ± 2.5 years. After adjusting for covariates including age, BMI, and mean arterial pressure, linear mixed-effects regression models showed that PWV was an independent determinant of the longitudinal increase in SBP. In a subset of 306 subjects who were normotensive at baseline, hypertension developed in 105 (34%) during a median follow-up of 4.3 years (range 2−12 years). By stepwise Cox proportional hazards models, PWV was an independent predictor of incident hypertension (hazard ratio 1.10 per 1 m/s increase in PWV, 95% confidence interval 1.00 to 1.30) in individuals with a follow-up duration greater than the median. PWV is an independent predictor of the longitudinal increase in SBP and of incident hypertension. This suggests that PWV could help identify normotensive individuals who should be targeted for the implementation of interventions aimed at preventing or delaying the progression of subclinical arterial stiffening and the onset of hypertension.

Longitudinal Perspective on the Conundrum of Central Arterial Stiffness, Blood Pressure, and Aging

Interactions among arterial stiffness, blood pressure (BP), and aging over time present a complex conundrum. The unraveling of this conundrum is a major public health priority because both arterial stiffness and BP are risk factors for cardiovascular morbidity and mortality. Cross-sectional studies show that BP is strongly associated with PWV. BP is transmitted into the arterial wall, where its increase progressively stimulates the less distensible collagen fibers, thus resulting in a progressively stiffer artery. Therefore, the age-associated increase in arterial stiffness has long been considered to parallel the age-associated increase in BP. Yet, the rates at which PWV and BP accelerate within individuals who differ in age and sex is largely unknown. Definition of PWV and BP trajectories over time is required to unravel the conundrum of interactions of arterial stiffness and BP as age increases and is also required for correct power analysis and the age/sex composition of clinical trials aiming to intervene on PWV. We have used the BLSA's well-characterized collection of longitudinal PWV and BP data to describe the natural history of arterial stiffening in BLSA [17]. Between 1988 and 2013, we collected 2–9 serial measures of PWV in 354 men and 423 women of the BLSA, who were 21–94 years of age and free of clinically significant CV disease [17].

Rates of PWV increase accelerated with advancing age in men more than women, leading to sex differences in PWV after the age of 50 years (Figure 6.3). At ages greater than 50 years the rate of increase in SBP was less steep than that of PWV (Figure 6.3) in both sexes, not only SBP ≥ 140 mmHg but also SBP of 120–139 mmHg was associated with steeper rates of PWV increase compared with SBP < 120 mmHg. Furthermore, there was a dose-dependent effect of SBP in men with marked acceleration in PWV rate of increase with age at SBP ≥ 140 mmHg compared with SBP of 120–139 mmHg. Except for WC in women, no other traditional CV risk factors predicted longitudinal PWV increase. In conclusion, the steeper longitudinal increase of PWV in men than women led to the sex difference that expanded with advancing age. Age and SBP are the main longitudinal determinants of PWV, and the effect of SBP on PWV trajectories exists even in the prehypertensive range. Surprisingly however,

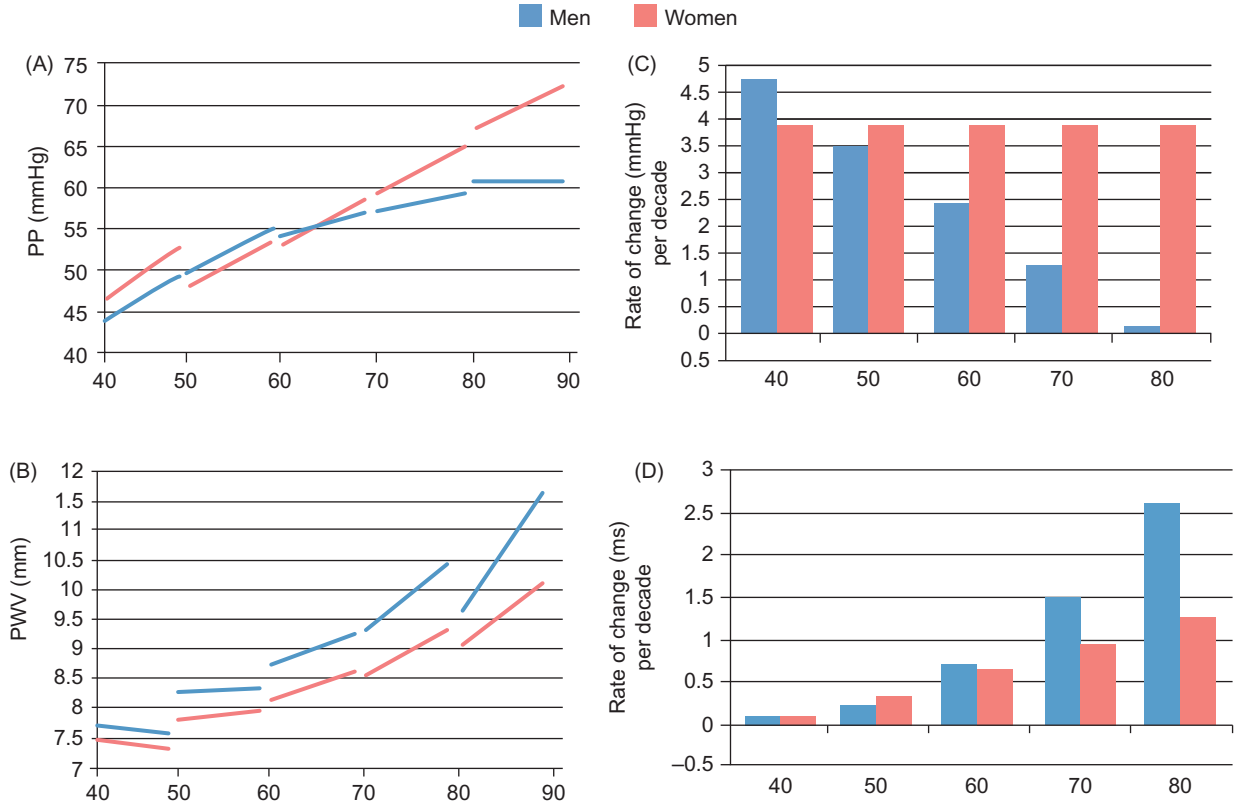

FIGURE 6.3 Concurrent longitudinal trajectories (left) and rate of change per decade (right) of (A) pulse pressure (PP) and (B) pulse wave velocity (PWV, m/s), from the Baltimore Longitudinal Study of Aging. There was dissociation in the trajectories of PP and PWV that is more pronounced in men.

the rates of change in PWV diverge in both sexes after the age of 50 years, as low rate of PWV continues to accelerate the rate at which SBP increases plateaus in women and decreases in men. Strikingly similar longitudinal trajectories of PWV and BP have emerged from the SardiNIA, a founder-based population study in which LCS conducts CV research [18].

The association of BP and aortic PWV is much more complicated than appreciated previously, possibly because of concurrent age-, sex-, and pressure-dependent aortic remodeling. PWV increases with time in men and women but, in men, this is not paralleled by an increase in systolic BP and pulse pressure (PP). The dissociation of the longitudinal changes in aortic PWV, systolic BP, and PP observed in BLSA indicates that PWV is not a surrogate for BP and that therapies to reduce PWV aimed primarily at BP reduction in older men may not be optimally effective. To delay age-associated arterial stiffening in humans and its attendant exponential increase in risk for arterial diseases, future interventional clinical trials need to begin to explore novel therapeutic strategies aimed at arterial wall mechanisms that are implicated in arterial stiffness. The definition of the rates of change in PWV and BP over time in individuals who entered the present study at different ages provides crucial information for the design of future proof-of-concept studies for interventions on arterial stiffening.

Impact of Traditional CV Risk Factors on PWV

Contributions of traditional CV risk factors to arterial stiffening were investigated in 247 healthy subjects from the BLSA, who were screened for the absence of ischemic heart disease, heart failure, and diabetic medications [19]. Thus, this study served as a starting point for future studies that could more specifically define risk factors for arterial aging. This study cohort included 104 men and 43 women. 51% had never smoked, 42% were former smokers, and 7% were current smokers. The age, gender, VO_2max, SBP, DBP, fasting blood glucose, total cholesterol, triglycerides, WC, BMI, and current smoking, but not HDL, were significantly associated with PWV. In a multiple regression analysis SBP, fasting blood glucose, and current smoking, but none of the lipid variable and neither of the body habitus measures, remained independently associated with PWV after adjusting for age, VO_2max, and their interaction. Thus, modifiable CV risk factors in addition to age are also independently associated with increased arterial stiffness. Hence, this provided the rationale for future studies to examine whether interventions aimed at treating or preventing these CV risk factors can attenuate the age-associated increase in arterial stiffness.

Central Obesity

Over the years, obesity has been postulated to have detrimental effects on CV health and BLSA has conducted several studies examining the impact of body fat and central adiposity on CV function. While studies had found that central obesity is associated with higher CF-PWV, the traveled distance (TD) of the pulse wave measured over the body surface can be substantially overestimated with wider WC. Thus, whether central obesity biases the estimation of PWV and whether this bias explains the association between PWV and different measures of adiposity was investigated. Seven hundred and eleven BLSA participants (49.5% men) who had PWV, anthropometrics, quantification of different fat deposits by computed tomography and dual X-ray absorptiometry were measured [20]. TD and relative PWV were estimated with a tape measure over the body surface or linear distances taken from radiological images, unaffected by obesity. A significant association was found between wider WC and a greater difference between the two TD measurements and their respective PWV in both sexes. This overestimation bias appeared to be generally higher in women than men (0.27 m/s for each unit increase in WC), when TD estimated over the body surface was used to calculate PWV; greater WC, total body fat, subcutaneous fat, and visceral fat were all associated with higher PWV. However, when PWV was calculated using TD estimated from radiological images or body height, only the association with visceral fat held significance. Thus, when TD is measured over the body surface, the role of obesity on PWV is substantially overestimated. However, even after accounting for this bias, PWV was still independently associated with visceral fat but not with other measures of adiposity, confirming its contribution to arterial stiffening.

Metabolic Syndrome

As noted above, MetS, also referred to as the insulin resistance syndrome, is defined as the clustering of several CV risk factors in an individual, including impaired glucose tolerance, hypertension, dyslipidemia, and abdominal obesity. Epidemiologic studies show that the MetS is quite common, affecting 24% of the US population between the ages of 20 and 70 years. Previous LCS studies had established that the MetS is a predictor of

adverse CV events, and thus we sought to investigate the role of MetS in age-associated arterial stiffness. The relationship between the MetS and large artery (common carotid) stiffness was evaluated in BLSA participants. We sought to evaluate whether the clustering of multiple components of the MetS has a greater impact on these vascular parameters than individual components of the MetS [21].

Carotid arterial stiffness was derived via B-mode ultrasonography in 471 participants from the BLSA who were without clinical CV disease and not on antihypertensive therapy. The mean ± SD age of the 200 men and 271 women was 59 ± 16 years. The prevalence of the MetS in this study population was 20.2%. MetS conferred a disproportionate increase in carotid stiffness (+32%) compared to controls. Multiple regression models, which included age, gender, smoking, LDL as well as each individual component of the MetS considered as continuous variables (abdominal circumference, triglycerides, HDL cholesterol, fasting glucose (FG), systolic and diastolic BP), showed that MetS was an independent predictor of stiffness. The presence of all five components of the MetS, however, was an independent predictor of stiffness. Separate models showed that higher order interaction terms among the components of the MetS were also independent determinants of stiffness, which lends further support to the notion that these interactions exert synergistic effects on the vascular endpoints. Thus, even after taking into account each individual component of the MetS, the clustering of at least three of these components is an independent predictor of vascular stiffness, and the clustering of all five components is an independent predictor of vascular stiffness. In other words, clustering of the components of the MetS has a synergistic detrimental effect on these vascular properties, and the greater the number of components in the cluster, the more pronounced the effect. It is thus conceivable that one of the mechanisms through which the MetS may exert its well-documented deleterious effects, is by adversely altering the structural and functional properties of the vasculature (such as thickness and stiffness altering).

Several population-based studies participating in the MARE (Metabolic Syndrome and Arteries Research) Consortium determined that the occurrence of specific clusters of MetS differed markedly across Europe and the USA [22]. BLSA participated in the MARE consortium to determine whether specific clusters of MetS are consistently associated with stiffer arteries in different populations. Data on 20,570 subjects from nine cohorts representing eight different European countries and the USA, including BLSA, participating in the MARE Consortium were analyzed. MetS was defined in accordance with NCEP ATPIII criteria as the simultaneous alteration in ≥ 3 of the 5 components: abdominal obesity, high triglycerides, low HDL cholesterol, elevated blood pressure, and elevated FG. PWV measured in each cohort was "normalized" to account for different acquisition methods. MetS had an overall prevalence of 24.2% (4,985 subjects). MetS accelerated the age-associated increase in PWV levels at any age, and similarly in men and women. MetS clusters TBW, GBW, and GTBW are consistently associated with equally stiff or significantly stiffer arteries to an extent similar or greater than observed in subjects with alteration in all the five MetS components—after controlling for age, sex, smoking, cholesterol levels, and diabetes mellitus—in all the MARE cohorts.

Advanced Glycation End Products

Assessment of advanced glycation end products (AGEs) could be used as an efficient diagnostic tool in a clinical setting, as they are easily obtained and quite measureable relative to other risk factors of CV disease. The relationship between AGEs and arterial stiffness had previously been examined in highly selected groups of patients with diabetes or hypertension. Our aim was to determine whether elevated serum AGEs are associated with increased arterial stiffness in relatively healthy, community-dwelling BLSA adults [23]. APWV and serum AGEs, as represented by the specific AGE, serum carboxymethyl-lysine (CML), were measured in 493 BLSA participants adults, aged 26–93 years. Mean (SD) PWV (m/s) was 6.6 (1.8) m/s. Mean CML was 0.47 (0.13) μg/mL. Serum CML (per 1 SD) was associated with PWV. After excluding all diabetic patients, after adjusting for age, sex, BMI, mean arterial pressure, fasting plasma glucose, HDL cholesterol, smoking, and other covariates serum CML (per 1 SD) was associated with PWV. Thus, elevated AGEs are associated with increased arterial stiffness, a known predictor of adverse CV outcomes, among relatively healthy BLSA adults. Interventions to lower levels of AGEs, such as altering the pattern of dietary intake, warrant examination as putative novel strategies to lower arterial stiffness in adults.

Plasma Vitamin D Levels

The importance of vitamin D for bone health has long been acknowledged. Recent evidence suggests that vitamin D can also play a role in reducing the risk of several other diseases, including CV disease. To test the

hypothesis that 25-hydroxyvitamin D (25-OH D) is an independent cross-sectional correlate of central arterial stiffness in a normative aging study population [24], we conducted a cross-sectional analysis in 1,228 healthy BLSA volunteers (50% males; age, 70 ± 12 years) of the BLSA. We measured CF-PWV and 25-OH D levels. We observed a significant inverse association between PWV and 25-OH D levels. After adjusting for age, gender, ethnicity, season of blood draw, estimated glomerular filtration rate, physical activity level, CV risk factors score (smoking, visceral obesity, hypercholesterolemia, hypertension, and diabetes), calcium/vitamin D supplementation, serum calcium, and PTH levels, the association between PWV and 25-OH D levels was only slightly reduced and remained statistically significant. Thus vitamin D levels are inversely associated with increased arterial stiffness in the BLSA population, irrespective of traditional risk factor burden. Further research is needed to understand the mechanism of this association and to test the hypothesis that vitamin D supplementation can reduce arterial stiffness.

Sex Hormones

Estrogen and Progestin Replacement in Postmenopausal Women

The incidence of hypertension in postmenopausal women exceeds that in age-matched men. Longitudinal studies relating hormone replacement therapy (HRT) to blood pressure changes are sparse. To investigate the association between HRT and longitudinal changes in blood pressure, we investigated [25] BP in postmenopausal women. Two hundred and twenty six healthy, normotensive postmenopausal women with a mean (± SD) age of 64 ± 10 years were followed for 5.7 ± 5.3 years. Seventy-seven women used both estrogen and progestin, and 149 used neither. Lifestyle variables, blood pressure, and traditional CV risk factors were measured at baseline and approximately every 2 years thereafter. SBP at baseline was similar in HRT users and non-users (133.9 ± 16.0 mmHg vs 132.4 ± 14.8 mmHg). Over time, average SBP increased less in HRT users than non-users, independent of other CV risk factors, physical activity, and alcohol use. Diastolic blood pressure, which did not change statistically over time in either group, was not associated with HRT. Thus, postmenopausal women taking HRT have a smaller increase in SBP over time than those not taking HRT. This difference is intensified at older ages.

In a subsequent analysis [26], both BP and aorto-femoral PWV were measured in 134 postmenopausal BLSA women, aged 51−90 years, screened to exclude clinical and occult CV disease, and classified as ERT non-users ($N = 57$) or ERT users ($N = 77$). The latter group was further substratified according to the use of estrogen alone ($N = 32$) or a combination of estrogen and progestins ($N = 45$). ERT users showed similar body habitus, physical activity, and plasma lipids compared to non-ERT users. ERT was associated with an average 9.8 mmHg lower systolic BP, and a 6.3 mmHg lower PP than in non-users. Multiple regression analysis showed that ERT was an independent predictor of lower SBP and PP. By analysis of covariance, ERT predicted a reduced age-associated increase in SBP, PP, and PWV. When systolic BP was >130 mmHg, the combination of ERT and progestins predicted a higher PWV than ERT alone. In conclusion, ERT in postmenopausal women can beneficially affect the vascular system, by reducing BP and the age-associated increase in arterial stiffness. The addition of progestins to ERT may reduce these beneficial effects.

Androgenic Hormones

Circulating testosterone levels (*T*) decrease with age in men and a Low *T* has been associated with coronary disease and with risk factors for atherosclerosis. We examined the relationship between androgenic hormones and carotid arterial stiffness, a major risk factor for CV events was evaluated in BLSA men [27]. In 901 men from the BLSA *T*, sex hormone−binding globulin (SHBG), and DHEAS were measured longitudinally over 33 years (follow-up 11.8 ± 8.3 years), of whom 206 (68.1 ± 13.7 years) underwent carotid duplex ultrasonography. The 901 men were used to characterize age-associated hormone levels by means of mixed-effects models. Hormone values were estimated from 33 longitudinal samples for the 206 men at the time of ultrasonography. Free *T* index (FTI) was calculated by dividing *T* by SHBG. The arterial stiffness index was calculated from peak systolic and end diastolic diameters of the common carotid artery and simultaneous brachial artery BP. *T*, FTI, and DHEAS were correlated negatively with age, PP, and stiffness index, whereas SHBG was correlated positively with age and stiffness index. However, *T* was the only hormone that predicted the stiffness index after adjustment for age, PP, fasting plasma glucose, BMI, and total cholesterol. *T* values 5−10 years before the carotid study also predicted

the stiffness index. Thus the adverse influence of low T on the CV system in men may be mediated in part via the effects of T on arterial structure and function.

Alcohol Consumption

In addition to exploring possible avenues such as HRT and vitamin supplements as interventions for CV disease, another equally important avenue was to explore lifestyle interventions such as diet; BLSA examined the impact of alcohol consumption on arterial stiffness [28]. A total of 563 volunteers were studied with carotid duplex ultrasonography with measurements of carotid arterial stiffness index, defined as ln (SBP/DPB)/(delta d/D), where SBP and DBP are systolic and diastolic blood pressures, delta d is the difference between systolic and diastolic diameters, and delta d/D is the average carotid artery strain. Alcohol intake was assessed by questionnaire. A U-shaped relationship was found between alcohol intake and stiffness index, with the lowest index in moderate drinkers (1−9.9 drinks per week); this relationship persisted after adjustment for CV risk parameters. Older age was associated with a higher stiffness index and intimal−medial thickness (IMT). Moderate drinkers showed 50% less age-associated increase in arterial stiffness than heavy drinkers and nondrinkers, both before and after adjusting for other CV risk factors. The alcohol effects persisted when beer, spirits, and wine were examined separately. Thus, light to moderate alcohol intake favorably modulates aging of the arterial tree. This effect may explain in part the J- or U-shaped relationship between alcohol intake and CV disease.

Suppressed Anger

Numerous studies have implicated trait anger and hostility in the pathogenesis of coronary heart disease; however, not many studies explored the impact of such factors on arterial stiffness. The associations of anger frequency (trait anger), expression (anger-out), and suppression (anger-in) with carotid artery stiffness were examined in younger and older healthy volunteers from the BLSA [29]. Carotid stiffness was derived from the stiffness index (SBP/DBP) high). Anger was evaluated with the validated Spielberger Anger Expression Inventory, a 44-item questionnaire that assesses anger frequency (trait anger), anger expression (anger-out), and anger suppression (anger-in). The mean ± SD age of the 126 women and 94 men was 57 ± 14 years. To evaluate the independent association between anger-in and stiffness, a multiple regression analysis was performed that included age, gender, race, BMI, SBP, anger-in, and the interaction between age and anger-in as the independent variables. After stepwise backward elimination, only age and anger-in remained independently associated with carotid arterial stiffness. Thus, anger suppression is an independent determinant of carotid arterial stiffness. Whether behavioral interventions focusing on anger expression can be effective at improving reversing arterial stiffness and its attendant CV risks deserves further evaluation.

ARTERIAL STIFFNESS AS EARLY MARKERS FOR SUBSEQUENT CV EVENTS IN ASYMPTOMATIC BLSA PARTICIPANTS

CV Disease Events

Increased arterial stiffness had been shown to be independently associated with adverse CV outcomes in patients with hypertension and with end-stage renal disease. We sought to evaluate the prognostic significance of APWV, and PP, two noninvasive indexes of arterial stiffness on CV outcomes, in healthy BLSA participants [30]. Participants from the BLSA were randomly selected to undergo carotid femoral PWV measurements. This analysis included 504 subjects (age range 20−96 years, 45% men, 78% Caucasian) with complete data, who did not have a preexisting MI or stroke, were not on diabetic meds, and with at least 2 years of follow-up. After a mean follow-up of 6.2 ± 2.9 years, 24 subjects had a clinical event, ascertained by reviewing medical records and death certificates. There were 17 deaths, of which 7 were due to CV disease. Four subjects sustained a nonfatal MI, 1 had a stroke, and 2 underwent coronary revascularization. Unadjusted Cox regressions showed that age, PP, PWV, FG, and white blood cell count were associated with all clinical events, and that these variables and LDL were associated with CV events (defined as clinical events less non-CV causes of death).

CV Event Prediction in an Individual Participant Meta-Analysis of Prospective Observational Data

Several studies have shown that a PWV may be a useful risk factor for predicting CVD, but they have been underpowered to examine whether this is true for different subgroups. The risk of PWV was assessed in a

systematic review and used individual participant data from 16 studies, including BLSA [31]. Study-specific associations of a PWV with CVD outcomes were determined using Cox proportional hazard models and random effect models to estimate pooled effects. Of 17,635 participants, 10% had a CVD event. The results showed that consideration of a PWV improves model fit and reclassifies risk for future CVD events in models that include standard risk factors. PWV may enable better identification of high-risk populations that might benefit from more aggressive CVD risk factor management.

Cognitive Function

PP and PWV, markers of arterial stiffness, have been associated with stroke, dementia, and lowered levels of cognitive function. Longitudinal relations of PP and PWV were related to multiple domains of cognitive function among nondemented, stroke-free BLSA participants [32]. One thousand seven hundred and forty nine participants from the BLSA completed tests of verbal and nonverbal memory, attention, perceptuo-motor speed, confrontation naming, executive functions, and cognitive screening measures, as well as concurrent sphygmomanometric assessment of blood pressure (for derivation of PP) on one to eight occasions over 14 years. A subset of ≤ 582 participants also underwent a single baseline assessment of PWV and cognitive assessment on one to six occasions over 11 years. Results of mixed-effects regression models revealed a prospective decline on tests of verbal learning, nonverbal memory, working memory, and a cognitive screening measure among those with increasing levels of PP. Persons with higher baseline PWV also exhibited prospective decline on tests of verbal learning and delayed recall, nonverbal memory, and a cognitive screening measure. Markers of arterial stiffness are associated prospectively with cognitive decline before dementia. Aggressive treatment of risk factors associated with greater arterial stiffness may help preserve cognitive function with individuals' increasing age.

PP, a Surrogate for Central Arterial Stiffness and Albumin Excretion

Albumin excretion (AE) is increasingly recognized as a predictor of CV morbidity and mortality. Endothelial function is an important regulator of vascular stiffness that we had not extensively evaluated in the past. 24 h urinary AE is thought to be due to endothelial permeability. AE has been shown to be associated with arterial intimal medial thickening. We therefore hypothesized that AE may also be associated with arterial stiffening. The relationship between AE and PP, a surrogate marker of vascular stiffness, was examined in 668 healthy volunteers from the BLSA who were not on antihypertensive or diabetic medications [33]. Subjects underwent routine clinical examination and measurement of FG, cholesterol, and 24 h urinary AE (which was log transformed). Seven subjects were excluded because of macro albuminuria ($AE > 200\ \mu g/min$). The mean $\pm$ SD age was 57 ± 15 years, 45% were men, 74% were Caucasian, and 50% were smokers (former or current). ln AE was associated with PP in men, but not in women ($P = 0.6$). In a multiple regression analysis, only PP, smoking status, and BMI were independently associated with ln AE after adjusting for age, whereas race, mean blood pressure, heart rate, glucose, and cholesterol (triglycerides, LDL, HDL) were not. Thus, PP is an independent determinant of AE in men but not in women. This suggests a gender-specific association between AE and vascular stiffness. Whether AE may serve as a noninvasive marker of a spectrum of subclinical vascular diseases that are due to, or mediated by, alterations in endothelial function deserves further investigation.

AGE-ASSOCIATED CHANGES IN CAROTID INTIMAL–MEDIAL THICKNESS

Noninvasive measurements made within the context of several epidemiological studies indicate that the carotid wall intimal media (IM) thickness increases two- to threefold 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 6.2). An age-associated increase in IM thickening (Figure 6.2) is accompanied by both luminal dilatation and a reduction in compliance or distensibility, with an increase in vessel stiffness.

Early identification and preventive treatment for asymptomatic CAD can potentially lower the risk for subsequent symptomatic CAD. An association has been demonstrated between increased IMT and conventional atherosclerotic risk factors, including hypertension, diabetes, hyperlipidemia, and cigarette smoking. Furthermore, several studies have shown a significant association of IMT with not only cerebrovascular disease, but also with clinical CAD. Despite the association between increased IMT and clinically manifest CAD, it was unclear whether increased IMT can be detected in subjects with subclinical CAD, that is, in presenting asymptomatic persons

with the disease. As noted above, our early studies in BLSA have demonstrated the predictive value of exercise ECG is improved by a combined use of thallium scintigraphy, for example, a double positive test (ECG and thallium) in otherwise healthy asymptomatic individuals. The predictive accuracy of a double positive test is ≤50% with respect to the incidence of a first clinical coronary event within 5 years.

Because marked heterogeneity in IM thickness, however, occurs among individuals of a given age (Figure 6.2), we tested the hypothesis that IMT would be increased in asymptomatic subjects with exercise-induced myocardial ischemia [34]. CCA IMT was measured, by B-mode ultrasound in 397 healthy volunteers from the BLSA (age, 58.5 ± 15.8 years) with normal ECG responses to maximum treadmill exercise, 72 asymptomatic subjects (age, 66.1 ± 13.4 years) with exercise-induced horizontal or downsloping ST-segment depression 1 mm, and 38 subjects (age, 77.4 ± 7.8 years) with clinically manifest CAD as diagnosed by medical history and resting ECG. After adjustment for age, IMT values progressively increased from healthy subjects (no CAD) to asymptomatic subjects with positive exercise ECG (possible CAD I) alone to those with concordant positive ECG and thallium scintigraphic findings (possible CAD 2), who had virtually identical IMT to subjects with manifest (definite) CAD. Thus, IMT is increased in older subjects with asymptomatic myocardial ischemia as evidenced by exercise ECG alone or in combination with thallium scan. Carotid ultrasound may help to identify *asymptomatic* individuals (in risk factor trials) with a high risk for subsequent clinical CAD.

Intima–Media Thickness and Regional Cerebral Blood Flow in Older Adults

The relationship between the thickness of the carotid intima (IMT) and brain function remains unclear in those without clinical manifestations of cerebrovascular disease. Understanding the neural correlates of this vascular measure is important in view of emerging evidence linking poorer cognitive performance with increased IMT in individuals without clinical cerebrovascular disease. Seventy-three participants in the BLSA (70.9 years; SD, 7.3) were evaluated with carotid artery ultrasound and resting $^{15}OH_2O$ positron emission tomography [35]. After adjusting for age, gender, and gray and white matter volumes in the regions where IMT is related to regional cerebral blood flow (rCBF), we found that higher IMT was associated with lower rCBF in lingual, inferior occipital, and superior temporal regions. Higher IMT was also associated with higher rCBF in medial frontal gyrus, putamen, and hippocampal-uncal regions. Whereas women had lower IMT and mean arterial pressure than men, they showed more robust associations between IMT and rCBF. The relationship between IMT and rCBF was only minimally affected by additional adjustment for mean arterial pressure. Thus, IMT is related to patterns of resting rCBF in older adults without clinical manifestations of cerebrovascular disease, suggesting that there are regional differences in CBF that are associated with subclinical vascular disease.

Carotid IMT Predicts Cognitive Decline

Though clinical CV and cerebrovascular diseases are established risk factors for cognitive decline and dementia, less is known about the relations between vascular health and cognition among individuals without these diseases. Carotid IMT, a measure of subclinical vascular disease, is associated with concurrent decrements in cognitive function, but relatively little research has examined longitudinal relations between carotid IMT and prospective cognitive decline. Relations of carotid IMT to prospective trajectories of cognitive function were among 538 (aged 20–93, 39% male, 66% white) participants in the BLSA free of known cardiovascular, cerebrovascular, and neurological disease [36]. Examined participants underwent initial carotid ultrasonography and repeat neuropsychological testing on up to eight occasions over up to 11 years of follow-up. Mixed-effects regression analyses were adjusted for age, gender, race, education, mean arterial pressure, BMI, total cholesterol, smoking, depressive symptoms, and CV medication use. Individuals with greater carotid IMT displayed accelerated decline in performance over time on multiple tests of verbal and nonverbal memory, as well as a test of semantic association fluency and executive function. Thus, carotid IMT predicts accelerated cognitive decline, particularly in the domain of memory, among community-dwelling individuals free of vascular and neurological disease.

Depressive Symptoms and Carotid IMT in the Baltimore Longitudinal Study of Aging

Prior literature has identified inconsistent cross-sectional associations between depressive symptoms and carotid IMT in healthy persons, and existing longitudinal work has relied on depression assessment at a single

time point. The relation between longitudinal trajectories of depressive symptoms as well as history of significant symptoms and subsequent carotid IMT among participants enrolled in the BLSA were analyzed to assess longitudinal covariation of depressive symptoms and carotid IMT over two time points [37]. A total of 556 participants (303 women and 253 men), aged 20–93 years (mean ± SD = 55.8 ± 15.9 years), completed the Center for Epidemiological Studies-Depression (CES-D) scale from one to eight times over 1–15 years. Participants later underwent high-resolution B-mode ultrasonography to assess IMT of the far wall of the common carotid artery. A subset of these participants ($N = 68$) underwent reassessment of IMT an average of 3.9 years later. Linear and mixed-effects regression models were adjusted for sex, race, education, SBP, LDL cholesterol, BMI, diabetes, smoking, and antihypertensive, lipid-lowering, and antidepressant medications. There was no relation between trajectory of depressive symptoms or history of significant depressive symptoms and future carotid IMT. There was also no evidence for longitudinal covariation of depressive symptoms and IMT over time. Additional analyses similarly revealed a lack of significant associations. There is no association between depressive symptoms and carotid IMT in the present sample of healthy community-dwelling volunteers.

THE VASCULAR AGING: THE LINK THAT BRIDGES AGE TO EARLY ATHEROSCLEROSIS (THE *VALIDATE* STUDY)

Atherosclerotic CV disease disproportionately affects older individuals, and its incidence, prevalence, and severity all markedly increase with age *The VALIDATE Study* is an ongoing research initiative within the BLSA designed to address the critical question of why and how aging is associated with an increased prevalence of atherosclerotic disease. The overall goal of this initiative is to identify those age-associated vascular properties responsible for increased disease so that intervention strategies targeting these "risky" elements can be developed and tested. Physiologic vascular properties, electron beam computed tomography (EBCT)-defined extent of coronary atherosclerotic burden are measured, as well as magnetic resonance imaging (MRI)-defined extent of carotid atherosclerotic burden, in BLSA volunteers and patient populations. By relating the dissociation between physiologic and chronologic aging to atherosclerosis, we expect to define (and compare) "successful" versus "usual" versus "accelerated" CV aging.

The VALIDATE study is presently in progress. Detailed MRI of Carotid Structure and Blood Flow in subsets of VALIDATE subjects have been published (Refs [38–41]).

ARTERIAL–HEART COUPLING

As noted above, with advancing age large vessels dilate and their walls thicken and become stiffer and BP increases. Arterial–heart "coupling" is an important and largely under-appreciated determinant of cardiac performance. Normal arterial–heart vascular coupling determines optimal LV stroke work, cardiac efficiency, and ejection fraction. We therefore believe that much insight into the structural and functional alterations and adaptations of the CV system, as well as the CV reserve, may be gleaned from examination of the coupling between the heart and the vasculature in BLSA.

Numerous age-associated changes in CV structure and function in healthy, sedentary, community-dwelling humans of the BLSA between 20 and 90 years of age have emerged from LCS studies [42–83]. A unified interpretation of identified cardiac changes that accompany advancing age and their interaction with age-associated arterial changes in otherwise apparently clinically healthy persons is depicted in the schematic in Figure 6.4. Some cardiac changes are, at least in part, adaptive, and occur to some extent in response to arterial changes that occur with aging. With advancing age, the walls of the left ventricle increase in thickness, largely because of an increase in ventricular myocyte size and an increase in vascular impedance, and this helps moderate the increase in LV wall tension. Prolonged contraction of the thickened LV wall which maintains a normal ejection time in the presence of the late augmentation of aortic impedance, is preserved by systolic cardiac pumping function at rest. A downside of prolonged contraction is that myocardial relaxation at the onset of diastole is relatively more incomplete in older than in younger individuals and reduces the early LV filling rate in older versus younger individuals. Structural changes and functional heterogeneity occurring within LV tissue with aging may also

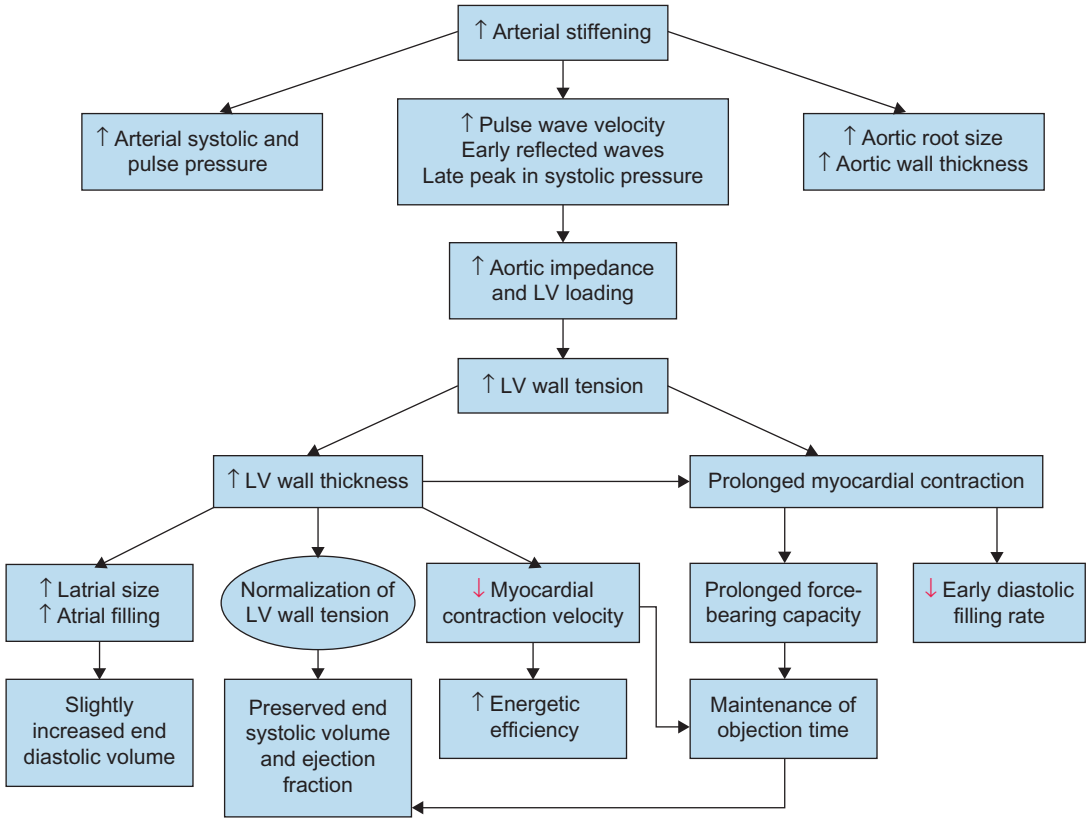

FIGURE 6.4 Arterial and cardiac changes that occur with aging in healthy humans.

contribute to this reduction in peak LV filling rate. Additional concomitant adaptations—left atrial enlargement and an enhanced atrial contribution to ventricular filling, however—compensate for the reduced early filling and maintain a normal end diastolic volume. A salient feature (Figure 6.4) are that the LV wall thickness increases (30% on average).

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