A Trilogy of Heart Disease Manifestations Emerges With Advancing Age

The preceding article in this series reviewed evidence as to why age-associated changes in the central arterial system are risky with respect to vascular disease. In a similar vane, the focus of this article is on the potential link between age-associated changes in the heart and clinical cardiovascular disease outcomes.

Left ventricular hypertrophy, heart failure, and atrial fibrillation increase dramatically with age (Figure 1). The prevalence of left ventricular hypertrophy (LVH) also increases with rising blood pressure and body mass index, a measure of obesity. Whether identified by electrocardiography or echocardiography, left ventricular hypertrophy has been shown to be associated with increased risk for coronary heart disease, sudden death, stroke, and overall cardiovascular outcomes.

It has been increasingly appreciated that the development of heart failure with apparently preserved systolic function, as evidenced by a “normal” ejection fraction, occurs in about one-third to one-half of older patients with heart failure. In a patient with heart failure, a diagnosis of diastolic heart failure can be inferred, largely by exclusion, when other comorbidities that masquerade as heart failure are ruled out and left ventricular ejection fraction is intact.

Atrial fibrillation (AF) is detected in approximately 3% to 4% of healthy volunteers over age 60 years who are rigorously screened to exclude clinical coronary artery disease; this is a rate 10-fold higher than in the general adult population. In the Framingham population, a history of AF without identifiable cause (so-called “lone” AF) was present in 16.8% of men and 6.0% of women with AF at a mean age of about 70 years. During long-term follow-up, individuals with lone AF suffered over 4 times as many strokes as control subjects, although their rates of coronary events or congestive heart failure were similar to those of controls. The proportion of AF cases that occur in the absence of an identifiable cause differs between studies. These differences are due to differences in characteristics of subjects and the rigor with which underlying causes are sought.

Age-Associated Changes in Cardiac Structure and Function in Persons Without a Heart Disease Diagnosis

There is a continuum of expression of cardiac structural and functional alterations that occurs with age in healthy humans, and these age-associated cardiac changes seem to have relevance to the steep increases in LVH, chronic heart failure, and AF seen with increasing age.

Cardiac Structure

Cross-sectional studies of subjects without hypertension or clinically apparent cardiovascular disease indicate that left ventricular (LV) wall thickness, measured via M-mode echocardiography, increases progressively with age in both sexes (Figure 2A). In older hospitalized patients without apparent cardiovascular disease, in whom overall LV mass was not increased, cardiac myocyte enlargement was observed at autopsy, along with an increase in the estimated myocyte number that was greater in males than in females. An increase in the amount (focal increases) and a change in the physical properties of collagen (purportedly due to nonenzymatic cross-linking) also occur within the myocardium with aging. The cardiac myocyte-to-collagen ratio in the older heart either remains constant or increases, however, because of an increase in myocyte size.

Left Ventricular Diastolic Function

The LV early diastolic filling rate progressively slows after the age of 20 years, so that by 80 years the rate is reduced, on average, up to 50% (Figure 2B). Structural (fibrous) changes within the LV myocardium or residual myofilament Ca²⁺ activation from the preceding systole (see below) are putative mechanisms for a reduced early diastolic LV filling rate. Despite the slowing of left ventricular filling early in diastole, more filling occurs in late diastole, due, in part, to a more vigorous atrial contraction (Figure 2C), which
produces an exaggerated A wave. The augmented atrial contraction is accompanied by atrial hypertrophy and enlargement and on auscultation is manifested as a fourth heart sound (atrial gallop). Multiple regression analyses indicate that age is the major determinant of the E:A ratio; hence, the age-associated decrease in the Doppler transmittal E:A ratio is identical in healthy Baltimore Longitudinal Study on Aging (BLSA) participant and in Framingham Study participants15,16 (Figure 2D).

Despite the age-associated changes in the diastolic filling pattern in older, healthy persons, their left ventricular end-diastolic volume index (end-diastolic volume normalized for body surface area [EDVI]) in the supine position is not compromised and does not substantially differ from their younger counterparts.17,18 Altered responses of cardiac volumes to postural maneuvers are associated with aging. Assumption of the sitting position from the supine position reduces EDVI in younger persons to a greater extent than in older ones.17 During short-term submaximal seated cycle exercise, EDVI increases equivalently at all ages, but during exhaustive exercise, EDVI drops to the seated rest level in younger men but remains elevated in older men.17 Thus, the average, acute, dynamic EDV reserve during the postural change and during graded upright exercise is moderately greater at 85 years of age versus 20 years of age. This does not support the widely held concept that LV filling is compromised in the older, “healthy” heart. In fact, during vigorous exercise, despite a reduction in the LV early diastolic filling rate,14 the LV at end diastole in healthy older persons is not reduced, but rather is greater in older than in younger men; in women, although EDV during exhaustive exercise is similar at older and younger ages, the change in EDV from rest to exercise significantly increases with age.17 Whether the capacity for further acute dilation of the LV of older persons is compromised has not been determined.

**Left Ventricular Systolic Function**

The LV ejection fraction (EF), the most commonly used clinical measure of LV systolic performance, is preserved during aging (Figure 3A). The average value of EF is approximately 65%, and very few healthy, sedentary, community-dwelling older individuals highly screened to exclude clinical and occult coronary disease have an EF <50%,17 a value indicative of impaired LV systolic function.10 The maximum EF, which is achieved during exhaustive upright exercise, decreases with age in healthy persons rigorously screened to exclude latent coronary disease (Figure 3B). Note that the heterogeneity in maximum EF in-
creases with age. The age-associated failure to augment EF with exercise is due to a remarkable age-associated deficit in the ability to reduce end-systolic volume index (ESVI); the acute ESV reserve (Figure 3C) at age 85 is only about one-fifth of that at age 20, and there is a similar age-associated loss of EF reserve.

The net result of the age-associated changes in EDV and ESV regulation during exercise is that the stroke volume index (SVI) is preserved in these older persons over a wide range of performance demand (Figure 3D) because of a greater use of the Frank Starling mechanism.17 Although healthy older persons use the Frank Starling mechanism during vigorous exercise, this mechanism is deficient because of an inability to appropriately reduce the ESV. Hence, although EDV increases to a greater extent during vigorous exercise in older versus younger persons, SV does not (Figure 3D).

Heart Rate and Cardiac Output

In the supine position at rest, the heart rate (HR) in healthy men does not change with age.17 With assumption of the seated position from the supine position, HR increases slightly, but significantly less in older than in younger men.18 The maximum heart rate during exhaustive, dynamic exercise decreases with age, and the magnitude of this age-associated reduction in peak HR is about 30% between 20 and 85 years of age (Figure 4A). The reduction in HR response to exercise is the reason why the maximum acute cardiac output reserve in healthy volunteers decreases, on average, by about 30% between ages 20 and 85 years (Figure 4B). Healthy individuals at the older end of the age range can augment their cardiac index 2.5-fold over seated rest, whereas those at the younger end of the age spectrum can increase their cardiac index 3.5-fold.

Figure 2. A, Left ventricular posterior wall thickness, measured by M-mode echocardiography, increases with age in healthy men and women in the BLSA. Reprinted from reference 33. B, Age-associated reduction in the early diastolic left ventricular filling measured via Doppler sonography in healthy volunteers in the BLSA. Reprinted from reference 16 and supplemented with measurements in additional BLSA volunteer subjects. The atrial contribution to filling is increased with aging. Reprinted from reference 16. D, The E/A decline with aging in healthy volunteers in the BLSA is identical to that participants of the Framingham Study. Reprinted from references 15 and 16.
The most reliable estimate of overall contractility is the slope of the ESP:ESV relationship as measured from pressure-volume loops obtained across a range of EDVs at rest. However, this has not been measured during exercise in a homogeneous, healthy study population of a broad age range, and by convention, this index cannot be assessed during exercise. A single point, depicting ESP:ESV ratio during exhaustive exercise (Figure 3D) as a crude “contractility” index suggests an age-associated decline in myocardial contractile reserve that is nearly identical to the defect in ESV regulation. Additional supporting evidence for a reduced LV contractile reserve that occurs with aging comes from studies in which the LV of older but not younger healthy men in the BLSA dilates at end diastole in response to a given increase in afterload in the presence of β-adrenergic blockade.

Sympathetic modulation of the cardiovascular system increases HR and contractility and redistributes blood to working muscles and skin to dissipate heat. All of the factors that have been identified to play a role in deficient cardiovascular regulation with aging, including HR (and thus filling time), afterload (both cardiac and vascular), myocardial contractility, and redistribution of blood flow, exhibit a deficient sympathetic modulatory component.

**Elaboration of Catecholamines**

During any perturbation from the supine basal state, apparent deficits in sympathetic modulation of these functions with aging occur in the context of exaggerated plasma levels of norepinephrine and epinephrine (see reference 21 for review) due to an increased spillover into the circulation, and, to a lesser extent, to a reduced plasma clearance in older versus younger persons. It has been suggested that deficient norepinephrine re-uptake at nerve endings is the primary mechanism for its increased spillover in older persons; the degree of spillover differs among body organs, but within the heart it increases with age. During prolonged exercise, however, diminished neurotransmitter re-uptake might also be associated with depletion, reduced release, and spillover. Thus, depending on the duration of the stress, enhanced or deficient neurotransmitter release might be a basis for apparent impairment of sympathetic cardiovascular regulation that occurs with aging.

**Impaired Responses to β-Adrenergic Receptor Stimulation**

The age-associated increase in neurotransmitter spillover into the circulation during acute stress implies a greater cellular receptor occupancy by these substances, which leads to desensitization of post-receptor signaling. Multiple lines of
evidence support the idea that the efficiency of post-synaptic β-adrenergic signaling declines with aging (see 21 for review). One line of evidence stems from the observation that acute β-adrenergic receptor blockade changes the exercise hemodynamic profile of younger persons to resemble that of older individuals. Significant β-blockade–induced LV dilatation occurs only in younger subjects (Figure 5A); the HR reduction during exercise in the presence of acute β-adrenergic blockade is greater in younger subjects than in older subjects (Figure 5B), as are the age-associated deficits in LV early diastolic filling rate, both at rest and during exercise (Figure 5C). It has also been observed that the age-associated increase in impedance during exercise in old dogs is also abolished by acute β-adrenergic blockade in old dogs.24 The second type of evidence for a diminished efficacy of synaptic β-adrenergic receptor signaling is that cardiovascular responses at rest to β-adrenergic agonist infusions decrease with age (see reference 21 for review).

**Left Ventricular Afterload and Vascular–Ventricular Load Matching**

Cardiac afterload has two components, one of which is generated by the heart itself and the other of which is generated by the vasculature. The cardiac component of afterload during exercise can be expected to increase slightly with age because the heart size increases in older persons throughout the cardiac cycle during exercise.17 The vascular load on the heart has 4 components: conduit artery compliance characteristics, reflected pulse waves, inertance, and resistance. There is considerable evidence to indicate that each becomes altered during aging and that at rest, the vascular load on the LV increases with age. Increased vascular loading on the heart is a likely cause of the increase in LV wall thickness associated with aging (Figure 2). Studies in large populations with a broad age range demonstrate that arterial pressure, which varies with vascular loading, is a major determinant of LV mass, and that the relative impact of age and arterial pressure on LV wall thickness varies with the manner in which study subjects are screened with respect to hypertension.25 The increase in LV wall thickness with aging reduces the expected increase in cardiac afterload because of increased LV volume in older persons during stress.17

Optimal and efficient ejection of blood from the heart occurs when ventricular and vascular loads are matched. It has been suggested that the precise cardiac and vascular load matching that is characteristic in younger persons is preserved at older ages, at least at rest, because the increased vascular stiffness in older persons at rest is matched by increased resting ventricular stiffness.26 Note that in this context, “stiffness” refers to time varying cardiac elastance throughout the cardiac cycle due to combined effects of contractile and structural properties. During exercise, however, a mismatch in loading occurs in older individuals because of a failure of LV elastance to increase in proportion to the increase in vascular elastance.27 Such LV arterial–ventricular load mismatching in older persons during exercise may be a mechanism for the deficit in the acute LVEF reserve that accompanies advancing age in many persons.

Acute reduction in both cardiac and vascular components of LV afterload has been achieved pharmacologically by administration of sodium nitroprusside (SNP) infusions in older, healthy BLSA volunteers. A reduction in resting mean arterial pressure of about 12% by SNP abolishes the greater carotid pulse pressure and heart size and augments exercise LVEF28 in these older subjects to levels observed in younger persons. The effect of physical conditioning to reduce vascular afterload is similar to the effect of conditioning to improve LV ejection in older persons.29

**Heart Rhythm**

Beat-to-beat fluctuation of HR, commonly known as HR variability, declines steadily with age (Figure 6A). Reduced HR variability is an indicator of cardiac autonomic regulation commonly found in older people and has been linked to increased risk for morbidity and fatal outcomes.30

An increase in the prevalence and complexity of both supraventricular and ventricular arrhythmias, whether detected by resting ECG, ambulatory monitoring, or exercise...
sons (solid line without points) rightward, but does not markedly offset the curve in older persons (dashed line without points). Thus, with respect to this assessment of ventricular function curve, β-adrenergic blockade with propranolol makes younger men seem like older ones. The abolition of the age-associated differences in the LV function curve after propranolol are accompanied by a reduction or abolition of the age-associated reduction in HR, which, at the maximum, is shown in B. Note, however, that β-adrenergic blockade in younger individuals (A) causes SVI to increase to a greater extent than during β-blockade in older subjects, suggesting that mechanisms other than deficient β-adrenergic regulation compromise LV ejection. One potential mechanism is an age-associated decrease in the maximum intrinsic myocardial contractility. Another likely mechanism is enhanced vascular afterload, due to the structural changes in compliance arteries noted above, and possibly also to impaired vasorelaxation during exercise. Reprinted from Fleg JL, Schulman S, O’Connor F, et al. Effects of acute β-adrenergic receptor blockade on age-associated changes in cardiovascular performance during dynamic exercise. Panels A and B reprinted from Ref 19. B, Peak exercise heart rate in the same subjects as in A in the presence and absence of acute β-adrenergic blockade by propranolol. C, The age-associated reduction in peak LV diastolic filling rate at max exercise in healthy subjects from the BLSA is abolished during exercise in the presence of β-adrenergic blockade with propranolol. Solid bars indicate age <40 years; light bars, age >60 years. Reprinted from reference 14.

Figure 5. A, Stroke volume index as a function of end diastolic volume index at rest (R) and during graded cycle workloads in the upright seated position in healthy men from the BLSA in the presence and absence (dashed line) of β-adrenergic blockade. R indicates seated rest; 1 to 4 or 5, graded submaximal workloads on cycle ergometer; and max, maximum effort. Stroke volume end-diastolic functions with symbols are those measured in the absence of propranolol; dashed and solid line functions without symbols are the stroke volume versus end diastolic function measured in the presence of propranolol. Note that in the absence of propranolol, the SV versus EDV relation in older persons (*) is shifted rightward in relation to that in younger ones (○). This indicates that the LV of older persons in the sitting position operates from a greater preload both at rest and during submaximal and max exercise compared with that of younger patients. Propranolol markedly shifts to the SV-EDV relationship in younger persons. Propranolol markedly shifts to the SV-EDV relationship in younger persons.

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Short bursts of paroxysmal supraventricular tachycardia (PSVT) are observed in 1% to 2% of apparently healthy individuals older than 65 years who were rigorously screened to exclude disease. Twenty-four–hour ambulatory monitoring studies have demonstrated short runs of this PSVT (usually 3 to 5 beats) in 13% to 50% of clinically healthy older subjects.11,31 Although the presence of nonsustained PSVT did not predict an increase in risk of a future coronary event in BLSA subjects, 15% of those with PSVT later developed de novo AF, compared with fewer than 1% of subjects without PSVT. The incidence of PSVT during exercise, typically asymptomatic 3 to 5 beat salvos, increases with age, from nil in the youngest age group to about 10% in the ninth decade (Figure 6B). Although those individuals with exercise-induced PSVT were not at a greater risk for coronary events over a multi-year follow-up, 10% developed a spontaneous atrial tachyarrhythmia compared with only 2% of the control group. Thus, PSVT at rest or induced by exercise is an early clue that some healthy individuals are at an increased risk for future AF. Another risk factor for AF may be the increase in left atrial size that accompanies advancing age in otherwise healthy persons.33

Limited data available in older subjects without apparent heart disease support a marked age-associated increase in the prevalence and complexity of ventricular ectopy (VE), both at rest and during exercise, at least in men. A steep increase in the prevalence of VE with advancing age occurs in both those clinically free of heart disease and in unselected populations. In healthy BLSA volunteers with a normal ST-segment response to treadmill exercise, isolated VE occurred at rest in 8.6% of men over the age 60 years compared with only 0.5% in those 20- to 40-years-old. Interestingly, in women, the prevalence of VE at rest was not age-related. Among 98 carefully screened asymptomatic BLSA participants older than 60 years, 35% had multiform VE, 11% had ventricular couples, and 4% had short runs of ventricular tachycardia on 24-hour monitoring; all occurred substantially more commonly in older subjects than in healthy younger subjects. Neither the prevalence nor the complexity of resting VE was a determinant of future coronary events over a 10-year mean follow-up period.32 Isolated VE during or after maximal treadmill exercise increased in prevalence 5-fold, from 11% to 57% between the third and ninth decades in apparently healthy BLSA volunteers (Figure 6C).
In summary, when cardiovascular function in healthy, adult, volunteer, community-dwelling subjects, ranging in age from 20 to 85 years, is assessed, increased LV wall thickness, alterations in the diastolic filling pattern, impaired LV ejection and HR reserve capacity, and altered heart rhythm are the most dramatic changes in cardiac function that occur with aging in healthy persons. Although these age-associated changes do not result in clinical heart disease per se, they do compromise the cardiac reserve capacity and affect the threshold for symptoms and signs, as well as the severity and prognosis of heart failure secondary to any given disease-related challenge. This is true for both systolic and diastolic heart failure. Thus, age-associated changes in the heart structure and function that occur in the absence of a clinical diagnosis of heart disease explain the increased risk for the 3 clinical conditions depicted in Figure 1: LVH, AF, and congestive heart failure, all of which occur at markedly higher rates in older persons than in younger persons. The 3 cardiac diagnoses become interrelated in older persons in part because of this link with age-associated cardiac changes. An age-dependent increase in left ventricular mass increases the stiffness of the left ventricle and promotes an increase in end diastolic filling pressure, which is an important contributor to diastolic heart failure in older persons. In addition, increased diastolic filling pressure results in left atrial dilation, which predisposes the heart to AF. AF, with associated tachycardia and loss of atrioventricular coupling, reduces diastolic filling time and eliminates atrial systolic contribution to left ventricular filling, thereby compounding the predisposition to diastolic heart failure.

The age-associated changes in cardiac properties described herein, as well as changes in vascular structure and function that accompany aging, which are the forms of topics discussed in the initial article in this series, alter the substrate on which cardiovascular disease is superimposed (Figure 7) in several ways, and thus alter the occurrence, presentation, and manifestations of heart disease in older persons. Age-associated changes in cardiovascular structure and function may lower the threshold for results in clinically significant signs and symptoms of disease (Table). For example, a mild degree of ischemia-induced relaxation abnormalities that may not induce clinical symptoms in a younger patient may cause dyspnea in an older one, who, by virtue of age alone, has preexisting slowed and delayed early diastolic relaxation. Similarly, a progressive decline in LV compliance with age may go unnoticed for many years (ie, subclinical diastolic dysfunction), but with the occurrence of an acute stress, the subclinical dysfunction can become acutely manifest as overt heart failure. A classic example is the development of AF with the loss of atrial contraction, coupled with abbreviated diastolic filling time due to tachycardia, which can precipitate pulmonary edema in a matter of minutes when the structural and functional milieu is present, as it is in the aging heart.

Age-associated changes in cardiovascular structure and function depicted below the “clinical threshold” line in Figure 7 ought not to be considered to reflect “normal” or “physiological” aging. Rather, these, in addition to other already acknowledged risk factors, might be construed as contributory factors to the diseases to which they relate. This is depicted below.
particularly relevant to extreme age-associated changes in cardiovascular structure/function that are perceived as deleterious aspects of cardiovascular aging in otherwise healthy persons but that ought to be interpreted to reflect “unsuccessful” cardiovascular aging. Indeed, data emerging from epidemiological studies indicate that specific aspects of cardiac and vascular aging in otherwise apparently healthy persons confer an increased risk for cardiovascular events. Age-related changes in vascular and cardiac structure and function are nearly ubiquitous. Central arteries stiffen with age, and this process raises systolic blood pressure and pulse pressure. Isolated systolic hypertension, the most common form of hypertension in older people, is associated with an increased risk for various manifestations of cardiovascular disease. In

### Relationship of Cardiac Human Aging in Health to Cardiac Diseases

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addition, the age-dependent increase in blood pressure contributes to increasing left ventricular mass, which has been identified as a risk factor for cardiovascular disease independent of the high blood pressure that may have contributed to its development. Congestive heart failure, a common and dire condition in the elderly, often is a late consequence of age-related alterations in blood pressure and cardiac and vascular structure and function.

In the future, accelerated heart and vascular aging in apparently healthy younger and middle-aged adults, ie, those who exhibit measurements of heart or vascular aging that usually occur later in life, may indicate the need for interventions designed to decrease the occurrence and/or manifestations of cardiovascular disease at later ages. Similarly, exaggerated heart or vascular aging in older persons, eg, those with age-associated vascular measurements in the upper tertile, may merit similar consideration. Specifically, prime targets for intervention are those persons presently perceived as normal individuals without a textbook cardiovascular diagnosis whose arteries and hearts are “unsuccessfully” placing them at increased risk for the occurrence of cardiovascular disease. Cellular and molecular clues as to why hearts and arteries of old persons “operate on the edge” are discussed in the subsequent article in this series.37

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References

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