Cardiovascular Aging

Lead Article

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CARDIOVASCULAR DISEASE
AND AGING

The proportion of the elderly in populations worldwide is increasing. It is estimated that by 2035 nearly one in four individuals will be 65 years of age or older. More successful recognition and treatment of cardiovascular risk factors and diseases continues to decrease age-adjusted cardiovascular mortality and increase the number and proportion of the elderly in the cardiac patient population. Cardiovascular diseases, such as coronary arterial atherosclerosis and hypertension and the resulting chronic heart failure, reach epidemic proportions among the elderly (Figure 1).

In the USA, cardiovascular disease is the leading cause of mortality, accounting for over 40% of deaths in those aged 65 years and over. Over 80% of all cardiovascular deaths occur in this age-group. These data indicate that age is the major risk factor for cardiovascular disease. The clinical manifestations and prognosis of cardiovascular diseases, as well as the heart failure that ensues, also worsen with increasing age.

Because hypertension, coronary atherosclerosis, and the resulting heart failure occur at exponentially increasing rates with advancing age, some gerontologists actually equate these cardiovascular diseases with an aging process. An alternative view is that these diseases are superimposed on the aging process itself, and that clinical practice in these patients essentially deals with the interactions between aging and disease (Figure 2). The horizontal line separating the upper and lower parts of Figure 2 denotes the clinical practice “threshold” for disease recognition. Thus, entities above the line are presently classified as “diseases that lead to heart and brain failure in older patients.” The vascular and cardiac changes presently thought to occur as a result of the “normal” or “physiologic” aging process (ie, those addressed in the previous sections) are depicted below the line.

The manifestations of certain cardiovascular diseases that lead to heart failure and stroke, such as atherosclerosis and hypertension, likely become altered in advanced age because of interactions that occur between age-associated cardiovascular changes in health and the specific pathophysiologic mechanisms underlying these diseases. These age–disease interactions result in a lower threshold for clinical symptoms, and greater severity and poorer prognosis of these diseases in older versus younger persons. In this regard, the cardiovascular changes that occur during healthy aging should not be considered to reflect a “normal process”; rather, these age-associated changes must be construed as specific risk factors for the aforementioned cardiovascular diseases, and should thus become the targets of interventions designed to prevent the epidemic of cardiovascular disease in the elderly. Such a strategy thus advocates preventive treatment for what is generally considered to be “normal cardiovascular aging.” Effective and efficient prevention of the “risks” associated with cardiovascular aging in apparently healthy individuals and with age–disease interactions in older patients requires a fundamental understanding of these age-associated changes. The present state of our understanding of age-associated changes in cardiovascular structure and function, from the molecular to the human scale, is the focus of this issue of Dialogues in Cardiovascular Medicine.

Keywords: aging; heart; vasculature; hemodynamics; molecular aging; cardiac structure; cardiac function; physical conditioning; cardiovascular disease; cardiovascular aging

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Quantitative information on these and other age-associated alterations in cardiovascular structure and function in healthy individuals is essential to define and target the specific characteristics of cardiovascular aging that render it such a major risk factor for cardiovascular diseases. This information is also required to differentiate between the characteristics of an elderly patient that relate to disease and those that are within expected “normal” limits. During the past two decades, a sustained effort has been applied to characterize the effects of healthy aging on many aspects of cardiovascular structure and function in a single study population. In the Baltimore Longitudinal Study on Aging (BLSA), community-dwelling volunteers were rigorously screened to detect both clinical and occult cardiovascular disease and were characterized with respect to lifestyle (eg, diet and exercise habits) in an attempt to clarify the interactions between these factors and changes that result from aging per se. The perspectives gleaned from these studies will be emphasized throughout this issue of *Dialogues in Cardiovascular Medicine*, as will relevant information from other studies in humans and using animal models.

### The left ventricular myocardium

As shown in Figure 3 (see page 70), cross-sectional studies of sedentary BLSA volunteer subjects without cardiovascular disease indicate that the left ventricular (LV) wall thickness, measured via M-mode (one-dimensional) echocardiography, increases progressively with age in both sexes (Figure 3A). At autopsy in elderly hospitalized patients without apparent cardiovascular disease and in whom overall LV mass decreased with age, cardiac myocyte enlargement was observed concurrently with an estimated decrease in myocyte number. The observed frequency of apoptotic myocytes, ie, those that undergo programmed cell death rather than necrosis, in the elderly heart is higher in men than in women, and apoptosis may partly contribute to the reduced number of myocytes in male hearts with aging. An increase in the amount of collagen and a change in its physical properties (purportedly due to nonenzymatic cross-linking) also occur in the myocardium with aging. However, the ratio of cardiac myocytes to collagen in the older heart either remains constant or increases.

An altered cardiac structural phenotype also evolves in rodents with aging. This includes an increase in LV mass, due to enlargement of myocyte size, and proliferation of the matrix in which the myocytes reside, which is focal in nature and may be linked to an altered cardiac fibroblast number or function. In rodents, the number of cardiac myocytes, which are postmitotic, terminally differentiated cells, also becomes reduced with advancing age. Putative stimuli for cardiac cell growth enlargement with aging in rodents are an age-associated increased vascular load due to arterial stiffening (see below) and an additional load due to stretching of cells caused by dropout of neighboring myocytes. The reduction in myocyte number may be attributable to apoptosis as well as necrosis. In fact, stretch per se is linked to cardiac myocyte apoptosis. Stretch of cardiac myocytes and fibroblasts releases...
growth factors, one of which is angiotensin II, which, in addition to modulating cell growth and matrix collagen production (and therefore cell size), also leads to apoptosis. An enhanced secretion of molecules like atrial natriuretic and opioid peptides, which are usually produced in response to chronic stress, is also observed in the senescent rodent heart.

**CARDIOVASCULAR FUNCTION**

**Cardiac volumes and ejection**

**Left ventricular filling and preload**

The end-diastolic volume (EDV) and myocardial fiber stretch are sometimes referred to as preload, which is a preexcitation determinant of myocardial function and pump performance. Preload is partly determined by ventricular filling characteristics, which are determined by the evolution of the atrioventricular pressure gradient during diastole. The LV early diastolic filling rate can be measured via echocardiography and Doppler ultrasonography. It progressively slows after the age of 20 years, and by 80 years the rate of...
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Figure 3. A. Left ventricular (LV) posterior wall thickness, measured by M-mode echocardiography, increases with age in healthy BLSA (Baltimore Longitudinal Study on Aging) men and women. B. Maximum early diastolic LV filling rate increases measured by equilibrium gated blood pool scans in healthy BLSA volunteers. C. Age-associated reduction in the early (E) diastolic LV filling measured via Doppler sonography in healthy BLSA volunteers. D. The atrial (A) contribution to filling is increased with aging. E. E/A declines with aging in healthy BLSA volunteers. EDV: end-diastolic volume.

Panel A is modified from reference 4; panel B is drawn from data in reference 5; and panels C, D, and E are modified from references 5 and 6.
is reduced by up to 50% on average (see Figures 3B and 3C). Structural (fibrous) changes within the LV myocardium or residual myofilament Ca$^{2+}$ activation from the preceding systole (see below) are putative mechanisms for a reduced early diastolic LV filling rate, since these increase LV pressure and thus reduce the atrioventricular pressure gradient. Contrary to much that has been written on the subject, a reduction in ventricular compliance with age remains unproven because an assessment of compliance requires the simultaneous determination of pressure and volume, which is not presently available in healthy young and elderly individuals. Despite the slowing of LV filling early in diastole, more filling occurs in late diastole, which is partly due to a more vigorous atrial contraction (Figure 3D). This produces an exaggerated A wave and a decreased E/A in the Doppler cardiogram (Figure 3E). The augmented atrial contraction is accompanied by atrial enlargement and is manifested on auscultation as a fourth heart sound (atrial gallop).

The acute reserve capacity of specific functions that determine cardiac performance can be conveniently illustrated by depicting them over a wide range of demand for blood flow and pressure regulation, eg, assumption of the sitting position from the supine position or during submaximal and exhaustive (maximum) upright exercise (Figure 4, see page 72). The lines depicted in the panels in the figure are the least-squares linear regressions on age of a given function in the steady state at different levels of effort in healthy, sedentary BLSA males. The overall magnitude of the acute, dynamic range of reserve of a given function in younger versus older subjects can quickly be gleaned from the length of the brackets depicted at the extremes of the regression lines.

Despite the age-associated changes in the diastolic filling pattern in older men, their LV end-diastolic volume index (EDVI), ie, end-diastolic volume normalized for body surface area in the supine position, does not substantially differ from their younger counterparts (Figure 4A). Aging affects the response of cardiac volumes to postural maneuvers. Assumption of the sitting position from the supine position reduces EDVI in younger, but not in older, individuals (Figure 4A); EDVI increases equivalently at all ages during submaximal seated bicycle exercise, and drops to the seated rest level during exhaustive exercise in younger men, but remains elevated in older men (Figure 4A). Thus, the average, acute, dynamic EDV reserve during postural change and graded upright exercise is moderately greater at 85 than at 20 years of age. This does not support the widely held concept that the filling of the heart with blood is compromised in the older, “healthy” heart, despite a reduction in LV early diastolic filling rate (Figure 3B). In fact, as Figure 4A illustrates, during vigorous maximal exercise, the left ventricle remains acutely dilated at end diastole in healthy, older individuals, but not in younger persons. The interindividual variation of EDVI within the age-associated patterns depicted during exhaustive maximal exercise by the regression line for men in Figure 4A is illustrated for both men and women in Figure 5A (see page 73).

It cannot be readily determined whether the capacity for further acute dilation of the left ventricle in older persons beyond that observed in Figure 4A is compromised. However, in older BLSA persons with occult silent coronary disease (manifest by both electrocardiographic [ECG] evidence and thallium scan perfusion deficits during exhaustive exercise, but not at rest), the LV EDVI at maximal exercise, but not at rest, is greater than that in healthy age-matched subjects, as is the increase in LV end-systolic volume index (ESVI) and reduction in ejection fraction (EF). Thus, at least in older patients with silent ischemia, the capacity exists for more acute LV EDV dilation during exercise than in healthy individuals.

**Left ventricular ejection**

Figure 4B illustrates the remarkable age-associated reduction in the reserve range of ESVI in younger men. ESVI becomes progressively reduced with increasing demands for cardiovascular perfusion from supine rest to maximal upright exercise. However, the range of acute end-systolic volume (ESVI) reserve at age 85 is only about a fifth of that at age 20. The age-associated failure in ESVI regulation across the various levels of demand that is depicted in Figure 4B causes a similar age-associated loss of EF regulation (Figure 4C). Figures 5B and 5C show the interindividual variations in ESVI and EF at maximal exercise in both men and women.

As a result of the age-associated changes in EDVI and ESVI regulation depicted in Figures 4A and 4B, the stroke volume index (SVI) is preserved in older individuals over a wide range of performance demand (Figure 4D). Specifically, in older men, the Frank-Starling mechanism (Figure 4A) produces a modest age-associated increase in SVI with the postural maneuver to an upright, seated posture at rest (Figure 4D). However, during progressive exhaustive exercise—
Figure 4. Least-squares linear regressions on age of left ventricular (LV) values, ejection fraction, heart rate, and cardiac index, at rest and during graded cycle exercise in 149 healthy BLSA (Baltimore Longitudinal Study on Aging) men who exercised to at least a 100-watt workload. *Indicates that regression on age is statistically significant. The overall magnitude of the acute, dynamic range of reserve of a given function in younger vs older subjects can be quickly gleaned from the length of the brackets depicted at the extremes of the regression lines. For end-diastolic volume index (EDVI), the average, acute, dynamic end-diastolic volume (EDV) reserve range during the postural change and during graded upright exercise is moderately greater at 85 than at 20 years. (A). There is a remarkable age-associated reduction in the range of reserve in the end-systolic volume index (ESVI) (B), which causes a similar age-associated loss of ejection fraction (EF) regulation (C). The stroke volume index (SVI) is preserved in older persons over a wide range of performance (D). However, during progressive exhaustive exercise, when in older men the failure to reduce ESVI (B) impairs the EF (C), SVI is not augmented in older vs younger men, as would be anticipated on the basis of their augmented EDVI. The maximum acute dynamic reserve range of HR is reduced by about one third between 20 and 85 years of age (E). The loss of acute cardiac output reserve from seated rest to exhaustive, seated cycle exercise averages about 30% in healthy, community-dwelling BLSA volunteer men (F). This reduction is entirely due to a reduction in HR reserve, as SVI at maximal exercise is preserved. At maximal exercise, the age-associated increase in EDVI is of borderline statistical significance in women. However, the change in EDVI from rest to maximal exercise in a given individual (not shown) significantly increases with age and is nearly identical in men and women.

Drawn from data in reference 18.
Figure 5. Scatter plots of cardiac volumes (A and B), ejection fraction (C), stroke volume (D), heart rate (E), and cardiac index (F) in the healthy sedentary BLSA (Baltimore Longitudinal Study on Aging) men depicted in Figure 3 and 113 BLSA women who exercised to a 75-watt workload. The figure illustrates the heterogeneity among individuals at a given age. In some instances, eg, heart rate, end-systolic volume index, and ejection fraction, this heterogeneity increases with age.

Drawn from data in reference 18.
when the failure to reduce ESVI (Figure 4B) impairs EF in older men (Figure 4C)\(^1\)\(^8\) — SVI is not augmented to greater levels in older than in younger men, as would be anticipated on the basis of their increased EDVI. In other words, while healthy older persons utilize the Frank-Starling mechanism during vigorous exercise, this mechanism is deficient due to impaired LV ejection. Figure 5D\(^1\)\(^8\) shows the interindividual variation of SVI in both men and women at maximal effort.

**Heart rate**

In the supine position at rest, the heart rate (HR) in healthy BLSA men is not age-related (Figure 4E).\(^1\)\(^8\) A reduction in the spontaneous and respiratory variations in resting HR is observed with aging and reflects altered autonomic modulation (see below). Upon the assumption of the seated resting position from the supine position, HR increases slightly less in older men than in younger men (Figure 4E).\(^1\)\(^8\) The magnitude of the age-associated reduction in HR increases progressively during exercise. The net result is that maximal acute dynamic reserve range of HR is reduced by about one third between 20 and 85 years of age. Figure 5E\(^1\)\(^8\) shows the interindividual variation of HR in both men and women at maximal effort.

**Cardiac output**

As expected from the behavior of the SVI and HR functions in Figures 4D and 4E, the supine cardiac index (CI) does not change with aging. During the postural maneuver, the age-associated increases in EDVI and SVI (Figure 4A and 4D) are balanced by an age-associated reduction in HR (Figure 4E). However, the loss of acute cardiac output reserve in healthy, community-dwelling, male BLSA volunteers during exhaustive, seated bicycle exercise averages about 30% between ages 20 and 85. This reduction is entirely due to a reduction in HR reserve, since at maximal exercise SVI is preserved in these healthy men, who were rigorously screened to exclude occult coronary disease at older age (Figure 4D).\(^1\)\(^8\) Alternatively stated, subjects at the older end of the age range can increase their CI 2.5-fold over seated rest, while those at the younger end of the spectrum can increase their CI 3.5-fold. Figure 5 shows the interindividual variation in the maximal cardiac output in BLSA men and women.

The hemodynamic patterns measured across the range of demands in Figure 4 are nearly identical in men and women. However, females do not exhibit a modest age-associated increase in EDVI in the seated position, because, unlike males, the assumption of the upright posture does not produce a greater reduction in EDVI in younger than in older women. Therefore, the SVI at seated rest does not increase with age in women, and, in contrast to men, the calculated CI at seated rest in women decreases modestly with age. At maximal exercise, the age-associated increase in EDVI is of borderline statistical significance in women. However, within a given individual, the change in EDVI from rest to maximal exercise (not shown) significantly increases with age, and the magnitude of this increase is nearly identical in men and women.\(^1\)\(^8\)

In summary, Figures 4 and 5 can be used to compare cardiovascular function in healthy, community-dwelling, adult volunteers aged 20 to 85 years: impaired LV ejection reserve capacity is the most dramatic change in cardiac pump function during healthy aging, as indicated by the failure of older individuals to regulate ESV (Figures 4B and 5B)\(^1\)\(^8\) as effectively as the young. This impaired ESV regulation is accompanied by diminished cardioacceleration, LV dilation at end diastole (Figures 4A, 4D, 5A, and 5D),\(^1\)\(^7\) and an altered diastolic filling pattern (Figure 3).\(^4\)\(^–\)\(^6\)

**INTERACTION OF PHYSICAL DECONDITIONING AND AGING**

It has become increasingly apparent that factors relating to lifestyle, eg, physical activity or nutritional habits, and the environment in which aging occurs, have substantial impact, not only on the exponential incidence of cardiovascular diseases in later life, but also on the “rate of aging” in the absence of disease. For example, it is widely recognized that a progressive physical deconditioning, eg, that attributable to a progressive reduction in physical activity, accompanies advancing age in most individuals living in industrialized societies. Thus, gerontologists and exercise physiologists have long debated whether some of the cardiovascular changes that accompany aging are simply caused by deconditioning rather than by an aging process per se. In this context, the issue arises as to whether physical conditioning via aerobic training of older sedentary persons can affect age-related deficits in cardiovascular reserve capacity.

It is well established that the peak oxygen consumption per unit of body weight (\(VO_2\) max) in healthy, sedentary BLSA individuals declines by about 10% per decade, or about 50% between the ages of 20 and 80 years.\(^2\)\(^0\) About half of this age-associated reduction in peak oxygen consumption, when measured during
upright bicycle exercise, is attributable to an age-associated reduction in cardiac function; the remainder is caused by diminished peripheral oxygen consumption accompanying age-associated reductions in muscle mass and strength, to inefficient redistribution of blood flow to working muscles, and/or to reduced oxygen extraction and utilization per unit of muscle.

It has been widely documented that the physical conditioning of older individuals can substantially increase their maximum aerobic work capacity and peak oxygen consumption. The extent to which this conditioning effect results from enhanced central cardiac performance or from augmented peripheral circulatory and O₂ utilization mechanisms, including changes in skeletal muscle mass, varies with the type and degree of conditioning achieved, the gender, the body position during study (see reference 21 for review), and likely on a genetic basis as well.

A longitudinal study in older males in the upright position indicates that an enhanced physical conditioning status increases O₂ consumption and work capacity, partly due to increases in the maximum cardiac output by increasing the maximum systolic volume (SV), and partly due to increases in the estimated total body (atrioventricular) O₂ utilization. The increase in maximum SV is due to a greater reduction in LV ESV (Figure 6) and a concomitant increase in LV ejection fraction (LVEF), as the effect of conditioning status to increase LV EDVI exercise is minimal (recall that in Figure 4A LV EDVI is already appreciably increased during acute vigorous exercise in older, sedentary, preconditioned men). This minor effect of physical conditioning on maximal exercise LV EDVI in older persons contrasts with the effect of physical conditioning in younger persons, in whom there is a substantial increase in EDVI and SVI during vigorous exercise on the basis of the Frank-Starling mechanism, as well as via an enhanced LVEF. In contrast to the improved LVEF, the maximum HR of older persons does not vary with physical conditioning status (Figure 6). Conditioning effects to improve LVEF in older persons appear to be related to effects to reduce vascular afterload (see below) and perhaps to enhance intrinsic myocardial contractility. In animal models, some, but not all, previously characterized determinants of intrinsic myocardial contractility are affected by physical conditioning status. There is presently no strong evidence that physical conditioning of older individuals can offset the age-associated deficiency in sympathetic modulation (see below).

**MECHANISMS OF DEFICIENT CARDIOVASCULAR REGULATION WITH AGING IN OTHERWISE HEALTHY PERSONS**

Ejection of blood from the heart (and hence the LV ESV and LVEF) is regulated across the range of demands for blood flow encountered in Figure 4 by changes in intrinsic myocardial contractility, afterload, and the autonomic modulation of both of these, with parasympathetic influences diminishing and sympathetic influences becoming more predominant with increasing demands for cardiovascular performance.

**Myocardial contractility**

In humans, information as to how aging affects factors that regulate intrinsic myocardial contractility is incomplete, because the effectiveness of intrinsic myocardial contractility in the intact circulation is difficult to separate from the effects of ventricular preload and afterload or from autonomic modulatory influences on contractility. A deficit in maximal intrinsic
contractility of older persons might be expected on the basis of the reduced maximum HR, as the HR per se is a determinant of the myocardial contractile state. Additional supporting evidence for reduced LV contractility with aging comes from studies in which the left ventricle of older, but not younger, healthy BLSA men dilates at end diastole in response to a given increase in afterload in the presence of β-adrenergic blockade.23

The most reliable estimate of myocardial contractility, i.e., the slope of the end-systolic pressure (ESP)/ESV ratio coordinates measured from pressure-volume loops across a range of EDVs at rest, has not been estimated in a homogeneous, healthy study population with a broad age range and, by convention, this index cannot be accessed during exercise. A single point, depicting ESP/ESV as a crude contractility index at each overall cardiovascular level of performance in Figure 3, suggests an age-associated pattern of myocardial contractile reserve that is nearly identical to the EF in Figure 4C.18

Most of our current information regarding age-associated changes in factors that regulate cardiac muscle or myocyte contractility is derived from studies in rodents. Coordinated changes in gene expression or protein function, which modify several key steps of cardiac muscle excitation–Ca2+ release–contraction relaxation coupling, occur in rodent hearts with aging and result in a prolonged action potential (AP), a pro-

**Figure 7.** Representative data depicting differences in various aspects of excitation–contraction coupling mechanisms measured between adult (6 and 9 months) and senescent (24 to 26 months) rat hearts. A. Transmembrane action potential.24 B. Isometric contraction.24 C. Cytosolic calcium transient, measured by a change in the luminescence of aequorin injected into several cells comprising the muscle preparation.25 D. Sarcoplasmic reticulum Ca2+ uptake rate.27

*Drawn from data in references 24-27.*
longed intracellular Ca\(^{2+}\) (Ca\(_\text{i}\)) transient, and a prolonged contraction (Figure 7D).\textsuperscript{24-26} Prolongation of the AP in senescent rats is not due to an age-associated increase in the L-type sarcolemmal Ca\(^{2+}\) current density. However, the L-type current inactivates more slowly and this could partly account for the prolonged AP.\textsuperscript{26} It is likely that reductions in outwardly directed K\(^+\) currents with aging also substantially contribute to AP prolongation.\textsuperscript{26} The rate of Ca\(^{2+}\) sequestration by the sarcoplasmic reticulum decreases in senescent myocardium (Figure 7D) and may partly explain the prolonged Ca\(_\text{i}\) transient.\textsuperscript{27} An age-associated reduction in the transcription of the gene coding for the sarcoplasmic reticulum Ca\(^{2+}\) pump, \textit{SERCA2}, could account for a decrease in the sarcoplasmic reticulum pump site density (see reference 21 for a review). The cardiac Na\(^+\)-Ca\(^{2+}\) exchanger (NCX1), which serves as the main transsarcolemmal Ca\(^{2+}\) extrusion mechanism, is more active in ejecting Ca\(^{2+}\) from cells of older versus younger hearts during diastole, and an increased NCX1 expression may partly compensate for a reduced sarcoplasmic reticulum pump function. The supporting evidence is that the abundance of NCX1 transcripts is increased by about 50% in the senescent (24-month) versus the young adult (6-month) rat heart.\textsuperscript{28} The prolonged Ca\(_\text{i}\) transient and contraction may impair myocardial relaxation during early diastole and may partly underlie the reduction in early diastolic filling rate that accompanies advancing age.

Marked shifts occur in the myosin heavy chain (MHC) isoforms, ie, the β-isoform becomes predominant in senescent rats and the myosin Ca\(^{2+}\)-adenosine triphosphatase (ATPase) activity declines with α-isoform (α-MHC) content (see reference 21 for review). The altered cellular profile, which results in a contraction that exhibits reduced velocity and a prolonged time course, can be considered to be adaptive rather than degenerative, because myocardial shortening at reduced velocity is energy efficient, and a prolonged contraction permits continued ejection for a longer period into the stiffened vasculature that accompanies advancing age (see below). Many of the multiple changes in cardiac excitation, myofilament activation, contraction mechanisms, and gene expression that occur with aging can be interpreted as adaptive in nature, because they also occur in the hypertrophied myocardium of younger animals adapted to experimentally induced chronic hypertension.\textsuperscript{21} There is evidence to suggest that the adaptive response to chronic pressure loading is reduced in older animals, possibly because some of the adaptive capacity of the heart is used as a response to the aging process.\textsuperscript{21} Excess myocardial Ca\(^{2+}\) loading leads to dysregulation of Ca\(^{2+}\) homeostasis, impaired contraction, arrhythmia, and cell death. The aged myocardium (and also that of young rodents chronically exposed to pressure over-load) exhibits a reduced threshold for pathologic manifestations of excess Ca\(^{2+}\) loading during stimulation (physiological and pharmacological), which increases Ca\(^{2+}\) influx, eg, in response to neurotransmitters, postischemic reperfusion, or oxidative stress.\textsuperscript{29} The cell Ca\(^{2+}\) load is determined by membrane structure and permeability characteristics, the intensity of stimuli that modulate Ca\(^{2+}\) influx or efflux via regulatory function of proteins within membranes, and reactive oxygen species (ROS), which affect membrane structure and function. Figure 8 (next page) shows that, notably, there is a reduced threshold for the occurrence of the manifestations of Ca\(^{2+}\) overload in senescent (24-month) versus younger adult (6- to 8-month) rat hearts during the stress of graded increases in the transsarcolemmal Ca\(^{2+}\) gradient. When bathed in 1.5-mM Ca\(_\text{o}\) and stimulated at 2.0 Hz, there is little or no difference in developed pressure (DP), end-diastolic pressure (EDP), resting pressure (RP), or half relaxation time (\textit{RT}_{1/2}) between old and young hearts (Figure 8A and 8B),\textsuperscript{29} and no aftercontractions (Figure 8C).\textsuperscript{29} The DP response becomes biphasic and Ca\(_\text{o}\) is progressively increased. The maximum increase in DP with increasing Ca\(_\text{o}\) is less in 24-month than in 6- to 8-month hearts (Figure 8A). Additionally, in 24-month hearts, the saturation and deterioration DP occur at a lower Ca\(_\text{o}\) than in younger hearts. Thus, the Ca\(_\text{o}\) response–systolic function curve is significantly shifted leftward in old vs young hearts.

EDP in the young hearts decreases slightly as Ca\(_\text{o}\) increases from 1.5 to 3 mM and then gradually increases back to the initial value as Ca\(_\text{o}\) is increased further (Figure 8A).\textsuperscript{29} However, in the 24-month hearts, a progressive elevation in EDP occurs with increasing Ca\(_\text{o}\). Moreover, as Ca\(_\text{o}\) increases, spontaneous diastolic cytosolic Ca\(^{2+}\) oscillations generated by spontaneous sarcoplasmic Ca\(^{2+}\) release occur asynchronously within and among myocardial cells. These become partially synchronized and cause aftercontractions, which occur more frequently in ventricular myocytes from senescent hearts than in young adult hearts (Figure 8C). The partially synchronized spontaneous Ca\(^{2+}\) oscillations that generate aftercontractions also cause afterdepolarizations, which are arrhythmogenic. Eventually, Ca\(^{2+}\) overload leads to ventricular fibrillation in most older hearts, but not in younger hearts (Figure 8D).\textsuperscript{29} Temporally summated, asynchronous spontaneous Ca\(^{2+}\) releases occurring within and among cells, or a steady
increase in diastolic Ca\textsuperscript{2+} within the cytosol, leads to incomplete diastolic myofilament relaxation (Figure 8C) and contributes to an increase in EDP (Figure 8A). Incomplete relaxation and increased diastolic tone is also observed in the senescent heart at physiological Ca\textsubscript{o} during higher pacing rates.\textsuperscript{30}

Cell remodeling is one cause of the relative Ca\textsuperscript{2+} intolerance of cardiocytes in the senescent heart. As noted, cells increase in size with aging, and changes occur in the amounts of proteins that regulate Ca\textsuperscript{2+} handling partly due to altered gene expression. Another cause of reduced Ca\textsuperscript{2+} tolerance of the older heart is
a change in the composition of membranes in which Ca\(^{2+}\) regulatory proteins reside, eg, an increase in membrane ω\(_6\)/ω\(_3\) polyunsaturated fatty acids (PUFAs) occurs with aging.\(^{31}\) A third cause is an enhanced likelihood for intracellular generation of ROS.\(^{32}\) In cells from the senescent heart.

**Vascular changes**

**Vascular structure**

With advancing age in healthy humans, the large arteries dilate (Figure 9A, see next page),\(^{4}\) their walls, particularly the intima, become thickened (Figure 9B),\(^{33}\) and changes occur within the vascular intima, which appear to resemble those that occur during early atherosclerosis. Collagen content increases and elastin becomes frayed. An increased elastase activity with aging may contribute to both elastin fragmentation and a reduction in its content with aging. While the macroscopic changes in vascular cells and the matrix of large vessels in humans are well described, the specific molecular mechanisms that lead to vascular stiffening and a thickened intima remain to be elucidated. In general, changes in resistance vessels with aging in healthy individuals are less well studied, but are apparently less marked than those in conduit arteries.

Age-associated macroscopic changes within large blood vessels in rodents are similar in many ways to those that occur in humans. Arterial remodeling with adult aging in rodents consists of dilation, medial thickening, and formation of an intima (see reference 12 for a review). Chronic morphological and biochemical modifications in the aortic intima of aging rats, ie, fragmentation of the internal elastic membrane and intimal thickening, and localized increases in growth factors and collagenase activity appear to be a muted version of alterations associated with chronic hypertension.

The thickened intima in older rats is composed of matrix molecules including collagen and proteoglycan, and vascular smooth muscle (VSM) cells. The thickened intima contains markedly high levels of the matrix metalloproteinase MMP-2.\(^{34}\) Metalloproteinases can mediate tissue breakdown and remodeling. VSM and endothelial cells are not terminally differentiated. VSM cells are subject to phenotypic modulation, during which they revert to a proliferative, secretory, and migratory mode. This “modulated” VSM cell phenotype repairs vascular damage and participates in vascular pathologies, such as hypertension and atherosclerosis. The intimal growth that occurs during aging resembles, in some ways, neointimal formation in response to arterial balloon catheter-induced injury. In fact, such neointimal growth is markedly enhanced in older versus younger rats, and this response is due to factors intrinsic to the vessel wall.\(^{35}\) Ample evidence indicates the occurrence of discontinuities in the internal elastic lamina in the aorta with advancing age in the absence of externally imposed experimental injury. Degradation of elastin by elastases and gelatinases (eg, MMP-2 and MMP-9) may be implicated in rupture of the elastic membrane.\(^{34}\)

Cytokine transforming growth factor-β (TGF-β) accumulates in the same regions of the intima of old rats as MMP-2. TGF-β, which suppresses protease activity and activates tissue inhibitors of MMP, is a potent factor in the synthesis of extracellular matrix proteins and its expression can lead to excessive fibrosis. Accumulation of TGF-β in the aortic wall of aged rats may account for the concomitant increase in fibronectin.\(^{34,36}\) There is some evidence to indicate that the collagenolytic and antiproliferative actions of TGF-β decrease with aging.\(^{38}\) Both fibronectin and TGF-β expression are regulated by angiotensin II.\(^{39}\) The fact that chronic administration of an angiotensin-converting enzyme inhibitor substantially reduces and delays the matrix and intimal changes associated with aging or hypertension suggests that age-associated changes in local vascular angiotensin regulation may have a role in the age-associated changes observed in TGF-β, fibronectin, and collagen deposition.

**Vascular afterload**

Cardiac afterload has two components, one generated by the heart itself and the other by the vasculature. The cardiac component of afterload can be expected to increase as a function of ventricular volume, eg, it increases acutely as the heart size increases during the various maneuvers in Figures 4 and 5.\(^{18}\) There is considerable evidence to indicate that the vascular load on the left ventricle at rest increases with age. The vascular load on the heart has four components: conduit artery compliance characteristics; reflected pulse waves; inertia; and resistance.

The age-associated structural changes in compliance arteries (Figures 9A and 9B)\(^{4,33}\) lead to a reduction in arterial compliance with aging. One manifestation of this is an increased pulse-wave velocity (PWV) (Figure 9C),\(^{40}\) which causes reflected pulse waves to reach the base of the aorta earlier in time, ie, prior to closure of the aortic valve, producing a late systolic augmentation of the central pressure-pulse contour (Figure 9D).\(^{40}\) Early reflected pulse waves, in conjunc-
Cardiovascular aging without a clinical diagnosis - Lakatta

**Aortic root size (mm.m⁻²)**
- Female: $r = 0.45, P < 0.0001$
- Male: $r = 0.42, P < 0.0001$

**Carotid wall thickness (mm)**
- Female: $r = 0.56, P < 0.0001$
- Male: $r = 0.56, P < 0.0001$

**Aortic pulse-wave velocity (cm.s⁻¹)**
- Female: $r = 0.61, P < 0.0001$
- Male: $r = 0.58, P < 0.0001$

**Carotid augmentation index**
- Female: $r = 0.57, P < 0.0001$
- Male: $r = 0.48, P < 0.0001$

**Systolic blood pressure (mm Hg)**
- Female: $r = 0.48, P < 0.0001$
- Male: $r = 0.29, P < 0.0001$

**Diastolic blood pressure (mm Hg)**
- Female: $r = 0.18, P = 0.0061$
- Male: $r = 0.068, P = 0.35$

**Pulse pressure/stroke volume index (mm Hg.mL⁻¹.m⁻²)**
- Female: $r = 0.37, P < 0.0001$
- Male: $r = 0.17, P = 0.02$

**Systemic resistance (mm Hg.L⁻¹.min⁻¹.m⁻²)**
- Female: $r = 0.37, P < 0.0001$
- Male: $r = 0.18, P = 0.02$
Cardiovascular aging without a clinical diagnosis - Lakatta

Figure 9 (opposite page). There is considerable evidence to indicate that the vascular load on the left ventricle at rest increases with age due to the age-associated structural changes in compliance arteries. A. Aortic root diameter in healthy BLSA (Baltimore Longitudinal Study on Aging) subjects measured via M-mode echocardiography. B. Carotid intima-media wall thickness measured in healthy BLSA subjects via echo-Doppler techniques. C. One manifestation of reduced arterial compliance (increased stiffness) is an increased pulse-wave velocity (PWV). D. With increasing age, the carotid pressure pulse exhibits a late peak, often observed as a second component. This is due to early reflected waves from peripheral sites, which are partly attributable to a reduced aortic compliance and increased PWV. The ratio of amplitude of the late component of the pressure pulse to the amplitude of the total pressure pulse is defined as the augmentation index. E. Early reflected pulse waves in conjunction with a resetting of the baroreflex lead to an increase in the resting systolic pressure with aging, which by definition, in normotensives, occurs within the clinically normal range. F. On average, the diastolic pressure does not increase after middle age (not shown), and in many older persons becomes reduced, due to the reduced conduit artery compliance and early reflected pulse waves occurring centrally in late systole rather than in diastole. G. The pulse pressure (PP)/stroke volume index (SVI) ratio, an index of large vessel stiffness, increases with aging. H. The total systemic vascular resistance, calculated from the resting mean arterial pressure and cardiac output, increases modestly or does not appreciably change at rest with aging in otherwise healthy persons. Panel A is modified from reference 4; panel B is drawn from data in reference 33; panels C and D are drawn from data in reference 40; panels E and F are modified from reference 41; and panels G and H are modified from reference 18.

...load matching that is characteristic in younger persons is preserved in the elderly, at least at rest, because the increased resting vascular stiffness with aging is matched by increased ventricular stiffness. One practical sequela of such matching at stiffer levels in older persons is that an acute reduction in LV preload would lead to a greater reduction in stroke volume and systolic arterial pressure in older individuals than in the young. Optimal and efficient ejection of blood from the heart occurs when the cardiac ventricular and vascular loads are matched. Whether optimal ventricular vascular coupling (load matching) is present during exercise in older individuals, however, remains to be determined.

Augmented LV afterload during exercise in older versus younger individuals likely plays a major role in the failure of the acute LV ESV reserve with advancing age (Figures 4 and 5B). However, the extent to which the age-associated increases in some afterload components at rest (Figure 9) become more pronounced changes during exercise is not known with certainty. While the acute cardiac dilation from the resting level that occurs during vigorous exercise in healthy older subjects points to a likely increase in their cardiac afterload, it has not been routinely possible to noninvasively assess PWV, the carotid arterial late pressure augmentation index (AGI), vascular diameter, or impedance during exercise. While some manifestations of afterload, eg, arterial pressure and total systemic vascular resistance (TSVR), have been measured during exercise, the range of these varies with the degree of effort achieved in exercise paradigms, such as those in Figures 4 and 5. The fact that maximum exercise capacity decreases with age confounds assessment of afterload via indices that require these exertion-dependent measures. It is noteworthy that the increases in PWV, carotid AGI, or pulse pressure that occur with aging are smaller in older persons who are physically conditioned than in sedentary persons. An effect of physical condition-
ing to reduce these components of vascular afterload appears to be involved in the effect of conditioning to improve LVEF (Figure 6).22

The impact of an acute reduction in both cardiac and vascular components of LV afterload on the LV ejection characteristics of older persons has been assessed pharmacologically.45 Sodium nitroprusside (SNP) infusion in older, healthy volunteers to lower resting mean arterial pressure by about 12%, abolishes the carotid AGI, reduces PWV and heart size, and augments LVEF (Figure 10)45 to levels achieved in younger persons. Systolic and diastolic arterial pressures during exercise in the presence of SNP are reduced, but exercise SVI is not affected, due to the reduction in preload; the maximum HR is also unaffected by SNP. Thus, while the maximal CI and workload deficits with aging in healthy persons are not reduced by SNP because of concomitant reductions in preload and afterload, the left ventricles of older persons could, nevertheless, in the presence of SNP, deliver the same SV stroke work (Figure 10)45 and cardiac output, while working at a smaller size in the presence of SNP. Verapamil also reduces exercise afterload, but not preload, in apparently healthy older volunteers and improves LV ejection and O2 utilization during submaximal exercise.43

Factors other than increased afterload are involved in the age-associated impairment of LVEF during exercise, as demonstrated during prolonged submaximal exercise, when afterload decreases progressively with time, rather than increasing as it does during incremental workloads in the study paradigms in Figures 4, 5, and 10.18,45 When individuals exercise at a constant submaximal work rate (50% of age-matched VO2 max) for prolonged amounts of time, i.e. 60 min or more, arterial pressure drops with time (Figure 11)46 and the estimate of arterial stiffness, pulse pressure/SVI, decreases with time to a similar extent in younger and older subjects (Figure 11).46 However, the concomitant time-dependent reduction in LV ESV and increase in LVEF in younger individuals (Figures 11D and 11E)46 exceed those in older individuals. Thus, the mechanism for the age-associated failure in the time-dependent improvement in LV ejection during prolonged submaximal exercise cannot be attributed to a failure of afterload reduction to occur with time, and other mechanisms limit the acute LV ESV reserve in these healthy, older persons. A clue to the nature of at least one of these other mechanisms comes from the concomitant failure of the time-dependent increase in HR of older subjects during prolonged submaximal exercise (Figure 11F).46 This is similar to the age-associated reduction in acute HR reserve during graded, incremental exercise (Figures 4 and 5).18

Deficits in sympathetic modulation

Efficient physical performance of the organism and optimal cardiovascular function require an efficient communication between the nervous and cardiovascular systems. Communication between these systems occurs largely via the autonomic nervous system. During vigorous physical activity, the modulatory role of the sympathetic component of the autonomic system prevails. The essence of sympathetic modulation of the
Figure 11. Whether factors other than increased afterload are involved in the age-associated impairment of left ventricular (LV) ejection during exercise can be assessed under prolonged submaximal exercise, during which afterload decreases progressively with time, rather than increasing, as it does during incremental workloads in the study paradigms in Figures 4, 5, and 9. When individuals exercise at a constant submaximal work rate (50% of age-matched VO2 max) for prolonged times, ie, 60 min or more, arterial pressure drops with time (A and B) and the estimate of arterial stiffness, the pulse pressure (PP)/stroke volume index (SVI) ratio, decreases with time (C), changing to a similar extent in both younger and older subjects. However, the concomitant reduction in LV end-systolic volume index (ESVI) and increase in LV ejection fraction (EF) and heart rate in younger individuals (D, E, and F) exceed those in the older individuals. The mechanism for the age-associated failure in the time-dependent improvement in LV ejection during prolonged submaximal exercise cannot be attributed to a failure of afterload reduction to occur with time and, thus, other mechanisms limit the acute LV end-systolic volume reserve in these healthy, older persons.

Drawn from data in reference 46.
The cardiovascular system is: (i) to ensure that the heart beats faster, (ii) to ensure that it retains a small size, by reducing the diastolic filling period, reducing LV afterload, and augmenting myocardial contractility and relaxation, and (iii) to redistribute blood to working muscles and skin so as to dissipate heat. All of the factors that have been identified to play a role in the deficient cardiovascular regulation with aging, ie, HR (and thus filling time), afterload (both cardiac and vascular), myocardial contractility, and redistribution of blood flow, exhibit a deficient sympathetic modulatory component.

Apparent deficits in sympathetic modulation of these functions with aging occur in the presence of exaggerated neurotransmitter levels. Plasma levels of norepinephrine and epinephrine increase during any perturbation from the supine basal state; this occurs to a greater extent in older than in younger healthy humans (see reference 47 for a review). The age-associated increase in plasma levels of norepinephrine results from (see reference 47 for a review). The age-associated increase in plasma levels of norepinephrine results from (see reference 47 for a review).

**Figure 12.** A. Stroke volume (SV) index as a function of end-diastolic volume (EDV) index at rest and during graded cycle workloads in the upright seated position in healthy BLSA (Baltimore Longitudinal Study on Aging) men in the presence (solid line) and absence (dashed line) of β-adrenergic blockade. R, seated rest; 1 to 4 or 5, graded submaximal workloads on bicycle ergometer; 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 functions measured in the presence of propranolol. Note that in the absence of propranolol in older persons the SV versus EDV relationship (A) is shifted to the right from that in younger ones (○). This indicates that the left ventricle of older persons in the sitting position compared with that of younger ones operates from a greater preload both at rest and during submaximal and maximal exercise. Propranolol markedly shifts the SV-EDV relationship to the right in younger persons (solid line without points), 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 appear like older ones. The abolition of the age-associated differences in the left ventricular (LV) function curve after propranolol is accompanied by a reduction in or an abolition of the age-associated reduction in heart rate, which, at maximum, is shown in B. Note, however, that β-adrenergic blockade in younger individuals in Figure B causes the stroke volume index (SVI) to increase to a greater extent than during β-blockade in older ones, suggesting that mechanisms other than deficient β-adrenergic regulation compromises LV ejection. One potential mechanism is an age-associated decrease in maximal 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.50 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 maximal exercise in healthy BLSA subjects is abolished during exercise in the presence of β-adrenergic blockade with propranolol. B and C: dark green ≤40 years; light green ≥60 years.5

Panels A and B are drawn from data in reference 50 and panel C is modified from reference 5.
The age-associated increase in neurotransmitter spill-over into the circulation during acute stress implies a greater receptor occupancy by these substances. Experimental evidence indicates that this leads to desensitization of the postsynaptic signaling. Indeed, multiple lines of evidence support the idea that the efficiency of postsynaptic β-adrenergic signaling declines with aging (see reference 21 for a review). One of these stems from the observation that acute β-adrenergic receptor (βAR) blockade changes the exercise hemodynamic profile of younger persons to resemble that of older ones. Significant β-blockade-induced LV dilatation only occurs in younger subjects (Figure 12A). Note, however, that β-adrenergic blockade in younger individuals causes SVI to increase to a greater extent than in older individuals (Figure 12), suggesting that mechanisms other than deficient β-adrenergic regulation compromise LV ejection. One potential mechanism is an age-associated decrease in maximum intrinsic myocardial contractility (see above). Another likely mechanism is enhanced vascular afterload in older subjects, due to the structural changes in compliance arteries and possibly also to impaired vasorelaxation during exercise. In this regard, it has been observed that the increase in impedance during exercise in elderly dogs is abolished by β-adrenergic blockade. The reduction in HR during exercise in the presence of acute β-adrenergic blockade is greater in younger than in older subjects (Figure 12B). The age-associated deficits in LV early diastolic filling rate, both at rest and during exercise (Figure 12C), also is abolished by acute β-adrenergic blockade. The second line of evidence for a diminished efficacy of synaptic βAR signaling is that cardiovascular responses at rest to β-adrenergic agonist infusions decrease with age (Figure 13, see page 86). Cellular mechanisms for the deficiency in βAR signaling in humans include a reduction in receptor number, affinity, and coupling to adenyl cyclase via Gβγ proteins. There is evidence that other G protein-coupled receptor signaling may also deteriorate in humans with aging (see reference 21 for a review). The efficacy of βAR subtype (ie, β1 vs β2 vs β3) signaling has not yet been studied in humans.

Studies in rodent models have delineated additional age-associated deficits in the β-adrenergic signaling cascade. A reduced contractile response to both β1AR and β2AR stimulation occurs with aging in isolated rodent LV muscle and in individual rat ventricular cardiocytes. This is due to failure of βAR stimulation to augment the intracellular Ca2+ transient to the same extent in cells from senescent hearts as in cells from younger adult hearts. The blunted increase in the Ca2+ transient following βAR stimulation in cells from older versus younger adult hearts is attributable to a decrease in the ability of either β1AR and β2AR stimulation to increase L-type sarcolemmal Ca2+ channel availability and thus to a lesser increase in Ca2+ influx via these channels, during the AP. The widely documented age-associated reduction in the postsynaptic response of myocardial cells to β1AR stimulation appears to be due to multiple changes in molecular and biochemical receptor coupling and postreceptor mechanisms. However, the major limiting modification of this signaling pathway with advancing age appears to be in the coupling of βAR to adenyl cyclase via the Gs (stimulatory) protein and to changes in adenyl cyclase protein per se, leading to a reduction in the ability to sufficiently augment cell cyclic adenosine monophosphate (cAMP) to drive the phosphorylation of key proteins that is required to alter protein function and augment cardiac contractility. The apparent desensitization of β1AR and β2AR signaling with aging is not mediated via increased βAR kinase (BARK) or increased G(i) (inhibitory) protein activity.

CONCLUSION

The age-associated changes in cardiac and vascular properties that are the focus of this issue of Dialogues in Cardiovascular Medicine alter the substrate upon which cardiovascular disease is superimposed in several ways (Table I, page 87). Age-associated changes may alter the manifestations and presentation of common cardiac diseases. This usually occurs in older patients with acute myocardial infarction in whom the diagnosis is delayed because of atypical symptoms resulting in increased time to initiation of therapy. Age-associated changes, including those in β-adrenergic responsiveness and vascular stiffness, also influence the response to and therefore the selection of different therapeutic inventions in older individuals with cardiovascular disease. Age-associated changes in cardiovascular structure function may lower the extent of disease severity required to cross the threshold that results in clinically significant signs and symptoms. For example, a mild degree of ischemia-induced relaxation abnormalities, which may be asymptomatic in a younger individual, may cause dyspnea in an older individual, who, by virtue of age alone, has preexisting slowed and delayed early diastolic relaxation. Thus, processes below the line ought not to be considered to reflect “normal” or “physiological” aging. Rather, they should be construed as specific risk factors for the diseases that they relate to, and thus be targets of interventions designed to decrease the oc-
Figure 13. A. Cardiovascular responses at rest to β-adrenergic agonist infusions decrease with age. The effect of rapid infusions of IV isoproterenol in increasing heart rate in healthy young and older men at rest.21 B. The effect of isoproterenol in increasing the left ventricular ejection in younger and older healthy men in the supine position before and after chronic endurance training. Endurance training had no effect on this index of cardiac pump function or on its response to isoproterenol.53 C. The contractile response to isoproterenol in left ventricular muscle isolated from potential donor hearts of older persons is reduced compared with that in similar preparations from younger individuals.54 D. Concentration–response curves to isoproterenol in single ventricular myocytes. Change in contraction amplitude is normalized to change produced by maximally stimulating concentrations of Ca²⁺ in the same cell. Results are from nonfailing hearts of young (≤40 years) and old (≥50 years) and hearts in severe end-stage failure (age = 45.8±4.7 years). NYHA, New York Heart Association.55 E. The effect of intra-arterial isoproterenol (isoprenaline) infusions to change the forearm vascular resistance in healthy younger and older men. Note that the drug effect reduces resistance, but the figure plots the effect as a change in resistance.56 F. The effect of IV infusion of isoproterenol in relaxing dorsal hand veins, previously constricted by phenylephrine, in men of varying ages.57

Drawn from data in references 21 and 53 to 57.
### Table 1. Relationship of cardiovascular human aging in health to cardiovascular diseases.

<table>
<thead>
<tr>
<th>Age-associated changes</th>
<th>Plausible mechanisms</th>
<th>Possible relation to human disease</th>
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<tbody>
<tr>
<td><strong>Cardiovascular structural remodeling</strong></td>
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| ↑ Vascular intimal thickness | • ↑ Migration of and ↑ matrix production by VSM cells
• Possible derivation of intimal cells from other sources | • Early stages of atherosclerosis |
| ↑ Vascular stiffness | • Elastin fragmentation
• ↑ Elastase activity
• ↑ Collagen production by VSM cells and ↑ cross-linking of collagen
• Altered growth factor
• Regulation/tissue repair mechanisms | • Systolic hypertension
• Left ventricular wall thickening
• Stroke
• Atherosclerosis |
| ↑ LV wall thickness | • ↑ LV myocyte size with altered Ca\(^{2+}\) handling
• ↓ Myocyte number (necrotic and apoptotic death)
• Altered growth factor regulation
• Focal matrix collagen deposition | • Retarded early diastolic cardiac filling
• ↑ Cardiac filling pressure
• Lower threshold for dyspnea
• ↑ Likelihood of heart failure with relatively normal systolic function |
| ↑ Left atrial size | • ↑ Left atrial pressure/volume | • Prevalence of lone atrial fibrillation and other atrial arrhythmias |
| **Cardiovascular functional changes** | | |
| Altered regulation of vascular tone | • ↓ NO production/effects | • Vascular stiffening, hypertension
• Early atherosclerosis |
| ↓ Threshold for cell Ca\(^{2+}\) overload | • Changes in gene expression of proteins that regulate Ca\(^{2+}\) handling
• ↑ ω\(_6\):ω\(_3\) polyunsaturated fatty acid ratio in cardiac membranes | • Lower threshold for atrial and ventricular arrhythmias
• Increased myocyte death
• Increased fibrosis
• Reduced diastolic and systolic function |
| ↓ Cardiovascular reserve | • ↑ Vascular load
• ↑ Intrinsic myocardial contractility
• ↑ Plasma levels of catecholamines
• ↑β-Adrenergic modulation of heart rate, myocardial contractility, and vascular tone due to postsynaptic synaptic signaling deficits | • Lower threshold for, and increased increased severity of, heart failure |
| **Reduced physical activity** | • Learned lifestyle | • Exaggerates age differences in some aspects of cardiovascular structure and function
• Negative impact on atherosclerotic vascular disease, hypertension, and heart failure |

LV, left ventricular; NO, nitric oxide; VSM, vascular smooth muscle.
currence and/or manifestations of cardiovascular disease in old age. Such a strategy would thus advocate the clinical treatment of “normal” aging per se. Specifically, prime targets for intervention are those “normal” individuals in Figures 3, 5, and 9.\textsuperscript{14,18} who appear to be aging less successfully than others. In other words, unsuccessful cardiovascular aging in the absence of a traditional clinical diagnosis ought to be construed as “subclinical” cardiovascular disease.

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Why is diastolic heart failure in older patients the cardiologist’s enigma?

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About 50% of patients in the older age range who have heart failure have normal systolic function. There have been several major barriers to understanding the pathophysiology and therapy of this important disorder in the elderly. The diagnosis of diastolic heart failure is largely one of exclusion. The pathophysiology of this disorder is incompletely understood, but it appears to share pivotal features with systolic heart failure, including reduced exercise stroke volume and cardiac output, increased filling pressure, and neuroendocrine activation. Patients with diastolic heart failure can have severe exercise intolerance, reduced quality of life, and significant morbidity and mortality. There are no large randomized trials with which to definitively guide therapy. Currently, therapy is empiric. Control of systolic blood pressure and left ventricular hypertrophy appear to be important.

In order to optimally manage patients with a specific disorder, clinicians must have access to detailed information regarding the following five key aspects of the disorder: epidemiology, pathophysiology, diagnosis, prognosis, and therapy. Diastolic heart failure (DHF) has recently been documented by several major epidemiological studies1-6 to account for one half of all heart failure cases among the elderly, who comprise three fourths of all heart failure cases.7 Despite this, there are few definitive published data regarding each of the above key aspects of this disorder. This leaves the clinician who recognizes this increasingly common disorder among his older patients with an enigma. How did we get into such a position?

Four factors have contributed to the remarkable disparity between the degree of importance of this disorder among the elderly and our knowledge regarding it: (i) lack of standard case definition; (ii) significant heterogeneity of the disorder; (iii) absence of a readily available, reliable test that characterizes and quantitates diastolic function; and (iv) the inherent difficulties in study-

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACEI</td>
<td>angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial</td>
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<tr>
<td>ATA</td>
<td>angiotensin-II antagonist</td>
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<tr>
<td>CHARM</td>
<td>Candesartan in Heart failure Assessment of Reduction in Mortality</td>
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<td>CHF</td>
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<td>diastolic heart failure</td>
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<td>LVEH</td>
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<td>left ventricular hypertrophy</td>
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<td>PEP-CHF</td>
<td>Perindopril in Elderly People with Chronic Heart Failure</td>
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<td>RAS</td>
<td>renin-angiotensin system</td>
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<tr>
<td>SHF</td>
<td>systolic heart failure</td>
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Diastolic heart failure in older patients - Kitzman

Diaphragm elderly subjects, including significant variability in the effects of aging on the cardiovascular system and presence of multiple concomitant other organ system disorders, discussed in detail above by Lakatta in the lead article of this issue of Dialogues in Cardiovascular Medicine. The difficulties are such that not long ago, some doubted whether DHF existed or was common. Several different names have been given for this syndrome, though there appears to be a convergence on the term DHF. Slowly, these barriers are being overcome and the pace of progress is increasing.

EPIDEMIOLOGY

In the Olmsted Community project, records were reviewed from all patients during a 1-year period in whom an assessment of left ventricular ejection fraction (LVEF) was obtained within 3 weeks of a new diagnosis of congestive heart failure (CHF). Mean patient age was 71 years and a normal LVEF was found in 43% of cases. Compared with those with reduced ejection fraction, patients with normal ejection fraction were much more likely to be women. Results from two large government-sponsored observational studies, the single-center Framingham Heart Study  and the multisite Cardiovascular Health Study  and other population-based databases also suggest that about 50% of elderly patients with CHF have DHF. Most reports have found DHF to be associated with female gender, older age, and a history of chronic systemic hypertension (Table I). 

DEFINITION AND DIAGNOSIS

Heart failure is a clinical syndrome and its diagnosis rests on a constellation of symptoms and signs. There is no single test that can confirm or exclude the diagnosis of heart failure, despite our frequently misguided reliance on LVEF measurement. Complicating the diagnosis of heart failure in the older patient are many other factors that are common in the elderly and that can cause dyspnea, fatigue, and edema, including chronic pulmonary disease, renal failure, obesity, anemia, and depression. Once one establishes the clinical diagnosis of heart failure, a mandatory initial step, how does one determine whether it is DHF? Four recent articles have attempted to clarify this.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Diastolic</th>
<th>Systolic</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
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</tr>
<tr>
<td>Gender</td>
<td>Mostly women</td>
<td>Mostly men</td>
</tr>
<tr>
<td>Age</td>
<td>Elderly</td>
<td>Middle aged</td>
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<tr>
<td>Racial distribution</td>
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<tr>
<td>History of hypertension</td>
<td>Nearly always</td>
<td>Often</td>
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<tr>
<td><strong>Pathophysiology</strong></td>
<td></td>
<td></td>
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<tr>
<td>Reduced peak exercise cardiac output</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Reduced peak exercise stroke volume</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Increased rest and exercise LV diastolic pressure</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Peak exercise end diastolic volume</td>
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<td>Increased</td>
</tr>
<tr>
<td>Peak exercise end systolic volume</td>
<td>Normal-decreased</td>
<td>Severely increased</td>
</tr>
<tr>
<td>Peak exercise heart rate</td>
<td>Mildly decreased</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>Resting left ventricular ejection fraction (LVEF)</td>
<td>Normal-increased</td>
<td>Severely reduced</td>
</tr>
<tr>
<td>Segmental wall motion abnormalities</td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (LVH)</td>
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<td>Eccentric or thinned</td>
</tr>
<tr>
<td>LV mass/volume ratio</td>
<td>Severely increased</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Neuroendocrine activation</td>
<td>Present</td>
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<tr>
<td>Peak exercise capacity (oxygen consumption)</td>
<td>Severely reduced</td>
<td>Severely reduced</td>
</tr>
<tr>
<td>Submaximal exercise capacity (anaerobic threshold)</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Aortic distensibility</td>
<td>Reduced</td>
<td>Reduced</td>
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</tbody>
</table>

Table I. Comparison of selected features of diastolic and systolic heart failure.
issue, each making an important contribution to this fundamental aspect of the problem.8-11

The typical DHF patient will be an older woman with long-standing or severe hypertension and will have concentric left ventricular hypertrophy (LVH) by echocardiography. DHF patients often have acute onset of symptoms and abrupt clinical deterioration associated with severe systolic hypertension.13,19,20 Jugular venous distention and pedal edema appear to occur less frequently than in systolic heart failure (SHF). Despite these generalities, the distinction between DHF and SHF cannot reliably be made at the bedside.21 Doppler techniques are not adequately specific to confirm the presence of diastolic dysfunction, particularly in the elderly.22 and invasive techniques that could be definitive are not practical in most patients.8,10,11,13 In this author’s opinion, DHF is a diagnosis of exclusion.13 First, the diagnosis of heart failure should be made on clinical grounds (symptoms and signs). Consideration should given to the host of other disorders that can cause similar symptoms in the elderly. Then, an echocardiogram should be performed to exclude significant systolic dysfunction (LVEF <50%). The echocardiogram also helps to exclude significant ischemic heart disease (akineti or thinned segments or multiple segmental wall-motion abnormalities); significant valve dysfunction; pericardial disease, hypertrophic obstructive cardiomyopathy, infiltrative cardiomyopathy (amyloidosis). Each of these specific disorders that can cause heart failure with a normal LVEF has important prognostic and therapeutic implications. In the absence of these, the patient has “isolated” DHF.

PATHOPHYSIOLOGY

The definition of heart failure—insufficient cardiac output to meet metabolic demands—suggests that there could be considerable overlap in the pathophysiology of DHF vs SHF (Table I). While numerous studies have intensively examined the pathophysiology of SHF, there are few data regarding the pathophysiology of DHF. Utilizing invasive cardiopulmonary exercise testing, one group of investigators demonstrated that patients with this syndrome have an inability to increase end-diastolic volume and stroke volume via the Frank-Starling mechanism despite severely increased left ventricular (LV) filling pressure, indicative of diastolic dysfunction (Figure 1).23 The resultant reduction in exercise cardiac output and early lactate formation are responsible for the severe exercise intolerance. Similar to SHF, exercise intolerance is the primary symptom in chronic DHF.13,14,23,24 Exercise hemodynamics in elderly DHF patients have been compared with those in patients with SHF.25 There was a similar degree of reduction in exercise workload, oxygen consumption, cardiac output, and stroke volume. In patients with SHF (mean LVEF 23%), the primary defect was markedly increased end-systolic volume that was partly compensated by an increased end-diastolic volume. In the patients with DHF, end-systolic volumes were normal and the major defect was markedly reduced end-diastolic volume and stroke volume responses. In both groups, pulmonary capillary wedge pressure was similarly elevated (mean 25 mm Hg). This comparison

Figure 1. Plot of pulmonary capillary wedge pressure versus left ventricular end-diastolic volume indicating the direction change from rest to peak exercise in 7 elderly patients with diastolic heart failure (open boxes) versus 10 age-matched normal controls (solid boxes). Note the shift upward and to the left denoting abnormal diastolic function.

demonstrated that, due to diastolic dysfunction, patients with DHF can have hemodynamic compromise during exercise that is just as severe as those with SHF.25

As discussed above, most DHF patients have systemic (specifically systolic) hypertension.17,18,21,23,26 It has been observed that severe hypertension is frequently present during the early phases of acute episodes of CHF in such patients and this was confirmed in a recent report.19 In animal models, diastolic dysfunction develops during the early phases of systemic hypertension due to increased afterload, and LV diastolic relaxation is very sensitive to increased afterload.27-29 In treatment trials of mild chronic hypertension, active therapy reduces the incidence of new heart failure by as much as 50%.30,31 It has also been suggested that increased blood pressure impacts upon mortality in patients with heart failure.26

A number of abnormalities in vascular function have been identified in patients with SHF, leading some to use the provocative term “vascular failure.” As reviewed by Lakatta above, increased vascular stiffness is a prominent aspect of cardiovascular aging. We recently found that older patients with DHF have an exaggerated increase in aortic stiffness beyond that of normal aging and that this may contribute to their exercise intolerance.32

It is well accepted that neurohormonal activation plays an important role in the pathophysiology of SHF. Clarkson et al showed that atrial natriuretic peptide and brain natriuretic peptide in DHF were substantially increased and that there was an exaggerated response during exercise, a pattern similar to that described in patients with SHF.33 Another report showed that plasma renin, aldosterone, and norepinephrine were increased in isolated DHF, though not as severely as in elderly SHF patients.34 These data suggest that neurohormonal activation may play a role in the pathophysiology of DHF.

Our current limited understanding of the pathophysiology of DHF suggests that therapeutic goals should include: (i) mild reductions in LV filling pressure, (ii) controlling systemic arterial pressure, (iii) LVH regression; (iv) improving LV (and possibly aortic) distensibility, and (iv) mitigating the effects of neuroendocrine activation.

**PROGNOSIS**

Elderly DHF patients appear to have substantial morbidity with frequent hospital admissions, with 3- and 6-month readmission rates of 29% and 43%, respectively.35,36 DHF in the elderly also appears to carry an appreciable mortality rate.3,37-39 In fact, the mortality rate appears to be similar to that of SHF when assessed in patients who are very elderly or who have had an acute hospital admission.37,38 For instance, Taffet et al37 examined a group of patients 75 years and older hospitalized for heart failure, and found a 28% mortality during the first year following the initial hospitalization, which then tapered off in subsequent years; there was no difference in the survival curves in patients with normal vs abnormal systolic function. Similar annual mortality rates were found by Aronow et al,39 Pernenkel et al,35 and Philbin et al.36 When assessed in nonhospitalized patients living in the community, the annual mortality rate appears significantly lower than in the above studies and, in this setting, mortality rates are lower for DHF than systolic heart failure. For instance, in both the Cardiovascular Heart Study and the Framingham Study, annual mortality rate was about 9% and was 2 times greater than case-controls, but only one half that of SHF subjects.2,3

**THERAPY**

It is remarkable that despite the high prevalence, substantial morbidity, and significant mortality of DHF, there are no prospective, randomized, blinded pharmacologic trial data to guide clinical decision-making.40 Given this fact, and that there is no agent with proven direct "lusitropic" properties, which of the available agents would theoretically be beneficial for DHF? Conceptually, those agents that have demonstrated benefit for SHF may hold the most promise, for two reasons. The first is that systolic contraction and diastolic relaxation are intimately linked and both are energy-dependent, require adenosine triphosphate (ATP), and are enhanced by beta-1-adrenergic agonists. The second is that regardless of whether due to systolic or diastolic LV dysfunction, the resulting low cardiac output should cause similar consequences, including neurohormonal activation, such that the pivotal heart failure pathophysiology may be similar in the two syndromes. The general goals of therapy in DHF are similar to those in SHF: to improve chronic exercise intolerance, hospital admissions for acute exacerbations, quality of life, and mortality. Specific targets of therapy theoretically include control of hypertension, ischemia, and tachycardia, and maintenance of sinus rhythm.

Chronic hypertension causes LVH and fibrosis, which impair diastolic chamber compliance. Acute hypertension significantly impairs diastolic relaxation. Control of hypertension may be the single most
important treatment strategy for DHF. In addition, meta-analyses indicate that therapy of chronic, mild hypertension is a potent means of preventing the development of heart failure. There are currently no data that favor one class of antihypertensive agent over others for this purpose, with the exception of doxazosin, which appears poorer than the three other agent classes tested in the ongoing Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). Ischemia is an independent therapeutic target and it markedly impairs diastolic relaxation. Loss of atrial contraction is deleterious to LV filling, and atrial fibrillation with fast ventricular rate is a common precipitant to decompensated DHF, such that avoidance of inappropriate tachycardia is important.

In the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for Evaluation and Management of Heart Failure, only diuretics and nitrates were recommended for therapy of DHF. Indeed, increased LV filling pressure is a frequent finding in DHF and is part of the definition of diastolic dysfunction. In addition, signs of pulmonary and systemic vascular congestion are frequent. Therefore, diuretics are often appropriate, although caution has been advised, because stroke volume may be highly preload-dependent.

Calcium channel antagonists are often proposed for DHF, although data are limited. In one small study of elderly men with clinical heart failure despite LVEF >45%, there was a 33% improvement in exercise time and significant improvements in clinicoradiographic heart failure scoring and peak filling rate. However, negative inotropic calcium antagonists can impair early relaxation, and in general have shown a tendency toward adverse outcome in SHEF. The newer dihydropyridine calcium channel antagonists appear to have somewhat better results in SHEF; however, no data are available in DHF patients.

β-Adrenergic blockers have also been proposed for DHF. These agents theoretically improve diastolic filling indirectly via negative chronotropy and increased diastolic filling time. However, in dogs, early diastolic relaxation is impaired by β-adrenergic blockade. On the other hand, several trials have shown substantial mortality reduction in SHF with the β-blockers, suggesting that these agents should be considered for inclusion in DHF treatment trials. β-Blockers do reduce blood pressure, regress ventricular hypertrophy, and increase the ischemic threshold, all of hypothetical importance in DHF. Importantly, a significant percentage of elderly patients have relative contraindications to β-blockers.

Most authors have advised against digoxin in DHF, because of an anecdotal report of deterioration, and because contractility is normal or even supranormal, and the therapeutic-to-toxic ratio with digoxin is small. However, in the Digoxin Investigators Group (DIG) study, patients with mild heart failure and normal LVEF had symptomatic improvement and no difference in mortality.

Angiotensin-converting enzyme inhibitors (ACEIs) and similar agents (such as angiotensin-II antagonists [ATAs]) that interfere with the renin-angiotensin system (RAS) and its end-organ effects are attractive for DHF. In SHF, they have proven efficacy in reducing mortality and hospital admissions, and in improving exercise tolerance and symptoms. As discussed above, there appears to be RAS activation in DHF. RAS inhibition controls hypertension and regresses LVH. In animal models of LVH, RAS activity is upregulated and increased myocardial tissue angiotensin I conversion impairs diastolic function. Increased RAS activity is a stimulus for myocardial fibrosis, which increases LV stiffness. In animals and in humans, angiotensin-converting enzyme inhibition improves LV relaxation and aortic distensibility.

Aronow et al showed in a group of elderly (mean age 80) patients with New York Heart Association (NYHA) class III symptoms and presumed DHF (LVEF >50%) that enalapril improved functional class, exercise duration, LVEF, diastolic filling, and LV mass. In an observational study of 1402 patients admitted to 10 community hospitals, ACEI use in DHF was associated with reduced all-cause mortality (odds ratio 0.61) and CHF death (odds ratio 0.55). In the Evaluation of Losartan In The Elderly–2 (ELITE-II) study in elderly SHF patients, compared with ACEI, ATA therapy resulted in less cough, but had similar rates of renal dysfunction and similar or slightly higher mortality. In a randomized crossover trial, the ATA losartan substantially improved exercise capacity (Figure 2, next page) and quality of life in patients with diastolic dysfunction, possibly by blocking the exercise-induced elaboration of angiotensin II and subsequently its adverse effect on LV relaxation. The ATA candesartan is being tested in a large multicenter mortality trial, Candesartan in Heart failure Assessment of Reduction in Mortality (CHARM). In addition, in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial, the ACEI perindopril is being tested in 1000 elderly CHF...
patients without major LV systolic dysfunction (LVEF <0.40). The primary outcomes are death and unplanned heart failure admissions, and secondary outcomes are quality of life and 6-min-ute walk time. Data are due to be reported in 2003.

A recent study demonstrated a substantial mortality reduction with low-dose spironolactone added to usual therapy in SHF. Because this agent appears to reduce interstitial fibrosis in cardiac and vascular tissue, it may be a candidate for testing in DHF patients as well.

Nonpharmacologic intervention is just as important in the patient with DHF as it is in SHF. The patient and family must thoroughly understand specific warning signs of worsening heart failure, the medication regimen, diet—especially moderate sodium restriction—and need for regular moderate physical activity. An accurate scale in the patient’s home, daily measurement of weight, easy and rapid communication to the doctor of unexpected weight gain, and timely adjustment of diuretic dosages are invaluable in preventing exacerbations. Moderate physical activity should be advised if feasible. Supervised exercise training in elderly patients with isolated DHF appears feasible and improves exercise tolerance and quality of life.

In the very elderly patients, who comprise most DHF, other goals may be more important than merely prolonging survival, including improving symptoms and quality of life, and preventing acute exacerbations and hospitalization.

**CONCLUSION**

Despite recent progress, patients with DHF probably represent the largest subset of cardiovascular patients for which diagnostic criteria are poorly defined and therapy is largely empiric. This is disconcerting given the importance of this syndrome for health care in the elderly. Until further data are available from well-designed pathophysiologic studies and from multiple large randomized trials, DHF will remain the cardiologist’s enigma.

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Exercise training improves aerobic capacity in elderly patients with diastolic heart failure: a randomized, controlled trial.
Artery changes with aging: degeneration or adaptation?

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Aging is responsible for important changes in vascular structure and function, which in turn affect the function of the heart and other organs. One of the main hallmarks of aging is large artery remodeling, which results in a progressive increase in wall thickness and lumen enlargement. Aging is almost always accompanied by atherosclerosis in humans, but these two processes differ in many aspects. Atherosclerosis is a disease that affects limited areas of the arterial tree and tends to narrow the lumen in the adult. Aging is a physiological process that affects the entire vascular system, starts after sexual maturation, and leads to enlargement of the lumen of large arteries. Vascular aging is characterized by degenerative processes, alterations in endothelial function, and arterial stiffening. These changes could reflect adaptive or degenerative processes.

One of the main hallmarks of arterial aging is arterial remodeling, which is the outcome of degenerative processes, but also involves adaptive, compensatory processes. As shown by Lakatta in the lead article of this issue of Dialogues in Cardiovascular Medicine, the age-associated structural changes in large arteries lead to a reduction in arterial distensibility. The ensuing increase in aortic pulse-wave velocity (PWV) results in an earlier reflection of pulse waves, which reach the aortic root prior to the closure of the aortic valves, thereby causing an increase in central systolic pulse pressure. This increased pulse pressure has been shown to be an independent cardiovascular risk factor. The mechanical arterial alterations due to aging thus have a deleterious effect. However, the increased pulse pressure is also associated with marked enlargement of the large arteries, which partly offsets the decreased arterial damping function, in spite of the increased wall stiffness.

Therefore, in order to fully understand the consequences of aging on arterial function, it is important to take into account the ability of the arterial system to adapt and compensate, or at least minimize, the deleterious effects of aging.

DEGENERATIVE PROCESSES

Degenerative changes and arterial remodeling

The mechanisms responsible for arterial remodeling have not been completely elucidated, but appear to chiefly involve elastolysis and disorganization of the extracellular matrix. Arterial aging is associated with extensive quantitative and qualitative changes affecting elastin, a major component of the extracellular matrix. Elastase activity was found to be increased in the plasma and arterial walls of old individuals, which could account for some of the observed alterations of elastic fibers. Elastic fibers from old animals and humans are disorganized, thinner, and more fragmented in comparison with those of younger individuals. Elastic fibers have a major support role in the arteries, and experimental alterations of elastin result in arterial dilation and formation of aneurysms. Finally, increased binding of calcium to elastin has been evidenced in the aorta of old rats, suggesting qualitative alterations in elastin properties.
Another important feature of age-related remodeling is the thickening of the intimal layer.⁷ ⁸ In the human aorta, a 2- to 6-fold increase in intima thickness between the ages of 20/40 years and 65 years or more has been evidenced.⁹ Compared with the young intima, the aged intima contains higher amounts of collagen, glycosaminoglycans, fragmented elastic fibers, smooth muscle cells (SMCs), and other mononuclear cells.⁷ ⁸ ¹⁰ ¹¹ Age-related intima thickening appears to be partly pressure-dependent, since it is stopped or reduced by experimental blood pressure reduction in rats.⁵ ¹² Media thickness increases with age in rats.² ⁶ ¹³ It should be noted that the effect of aging on media thickness is much less pronounced than that of experimental hypertension.¹² The increase in blood pressure associated with aging probably plays only a minor role in the development of media thickening. In normotensive nonobese WAG/Rij rats, aortic and carotid wall thickness was found to increase with age, although their arterial blood pressure remained remarkably delayed the effect of aging on the cardiovascular system.⁶

**Aging and endothelial dysfunction**

Aging is associated with multiple alterations in endothelial function, with important consequences in aged individuals. Alteration of endothelial control of vasomotor tone impairs the vascular adaptation to changes in flow, in particular those induced by exercise and ischemia. Moreover, alterations in macromolecular transport and in prostacyclin (PGI₂) synthesis may facilitate the development of atherosclerosis and thrombosis, the main determinants of cardiovascular diseases in elderly populations.

Endothelial cell turnover and DNA synthesis increase in aged animals, resulting in increased protein synthesis.¹⁴ The number of circulating endothelial cells, an indicator of their turnover, increases with age in rats.¹⁵ The barrier function of the endothelium was shown to deteriorate with age. In the aortas of 30-month-old rats, a 2-fold increase in endothelial permeability to albumin compared with 10-month-old rats was reported.¹⁶ This favors the passage of plasma macromolecules across the endothelium and their trapping in the intima,¹⁷ which could contribute to the development of age-related intimal modifications.

One of the major functions of the endothelium is to release vasoactive substances, including PGI₂, nitric oxide (NO), and endothelin:
- PGI₂ synthesis by human endothelial cells from aged donors was found to be reduced in comparison with young donors.¹⁸ In addition, a 3- to 4-fold decline in plasma levels of PGI₂ was documented in 60- to 70-year-old subjects, compared with 20- to 30-year-old subjects.¹⁹
- Arterial aging is associated with a marked impairment of endothelium-dependent relaxation, a response essentially mediated by NO. In old animals, acetylcholine-induced relaxation of preconstricted vessels is reduced compared with younger animals.²⁰-²³ In humans with angiographically normal coronary arteries, the changes in coronary blood flow and diameter following acetylcholine injection were found to be reduced with age.²⁴ ²⁵ The mechanisms accounting for impaired endothelium-mediated relaxation in aging have not been completely elucidated. In vitro NO production by rat aortic rings, directly measured by a microsensor technique, was found to be reduced with aging.²⁶ It was also suggested that NO had a limited access to medial SMCs.²⁷ Interestingly, advanced glycosylation end products (AGEs), which are present in the intima and inner media of aged arteries, were shown to quench NO,²⁸ suggesting they may play a role in the impairment of endothelium-dependent relaxation.

Most experimental studies indicate that aging is associated with a decrease in NO production and release. Endothelial NO synthase expression was found to be reduced in aorta from old rats compared with young rats,²⁹ ³¹ as a result of a decrease in wall content of cyclic guanosine monophosphate (cGMP), the intracellular messenger of NO.²⁹
- Endothelin exerts a contractile effect on vascular SMCs and potentiates the effects of other vasoconstrictors. Endothelin production and endothelin-converting enzyme activity in rat aorta were found to increase with age.³⁰

**Age-related changes in arterial stiffness and compliance**

Arterial stiffening is another hallmark of arterial aging. Arterial stiffness is assessed in humans by measuring the pressure/volume relationship in aortas from subjects deceased at different ages.³² Several studies using noninvasive techniques confirmed that human arteries become more rigid with advancing age.³³ ³⁵ Interestingly, age-related arterial stiffening has been evidenced in normotensive subjects, regardless of ethnic groups or differences in lifestyle.³⁵

The mechanical properties of the arterial system can be assessed by different methods, which yield different kinds of information.
Elastic modulus
The relationship between strain (relative increase in length) and stress is a basic and useful parameter that describes the stiffness of a tissue. The slope of the strain-stress relationship represents the elastic modulus of the arterial wall.

Compliance
In blood vessels, it is also important, from a physiological point of view, to determine the relationship between pressure changes and volume changes, in other words, compliance. The compliance of a chamber is an overall quantitative description of its wall properties; compliance (C) is defined as the change in volume (∆V) due to a change in pressure (∆P), i.e:

\[ C = \frac{\Delta V}{\Delta P} \text{ [mL/mm Hg]} \]

Therefore, compliance is determined not only by the mechanical properties of the wall but also by the geometry and size of the vessel.

Distensibility
Compliance can be referred to vessel volume at a given transmural pressure, yielding distensibility (D), which depends on arterial wall stiffness and not geometry:

\[ D = \frac{C}{VP} \text{ [mm Hg}^{-1}] \]

Pulse-wave velocity (PWV)
The traditional way of estimating distensibility of the arterial system in vivo consists in measuring arterial PWV (m/s). PWV gives roughly the same information as arterial distensibility:

\[ PWV^2 = \frac{VA\Delta P}{\rho \Delta V} \text{ [m/s]} \]

where \( \rho \) is the specific mass of blood.

Arterial stiffening and collagen alterations
In vivo arterial compliance depends both on extracellular matrix and on basal SMC contractile tone. In old rats, SMC poisoning by potassium cyanide results in a much smaller change in compliance than in young animals, indicating that the contractile component in stiffening of aged large arteries is minor. In contrast, alterations of the medial extracellular matrix play a major role in arterial stiffening. With aging, collagen density increases in the medial layer, while the amount of elastin remains stable or declines. Therefore, the elastin/collagen ratio, which is a key determinant of viscoelastic properties of the wall, decreases with age (Figure 1).

Moreover, nonenzymatic glycation processes modify the properties of collagen in aged arteries. Glucose has been shown to react with NH groups of proteins, leading to the formation of Schiff bases, Amadori products, and AGEs. Since this process is very slow, long-lasting proteins like collagen and elastin are more concerned than proteins with a high turnover. Increased glycation processes and AGE accumulation have been documented in the plasma and in the arteries of old individuals.

Figure 1. Changes in medial thickness and elastin/collagen ratio in the aorta (A) and (C), and the carotid artery (B) and (D) of rats of different ages. Differences between age-groups were significant for each parameter and arterial site. Systemic arterial compliance (E) and in situ carotid compliance at 100 mm Hg (F) significantly declined with age.
eral biological actions, one of which is the cross-linking of proteins of the extracellular matrix. These cross-links change the properties of collagen, which becomes more rigid, more resistant to proteolysis, and less soluble.39,41,44

**ADAPTIVE PROCESSES**

**Arterial enlargement: adaptation to wall stiffening?**

Arterial enlargement is consistently observed with aging. This can be considered as a compensatory mechanism for wall stiffening, since vessel compliance is the product of arterial wall distensibility and arterial volume. Thus, the decrease in distensibility that occurs with aging is partially compensated by the concomitant increase in vascular volume.

In a postmortem study, the diameter of human aortas, maintained at their operative in vivo blood pressure, was found to be increased by 15% to 20% and aortic volume by 30% to 40% in subjects older than 65 years, compared with younger subjects.9 The lengths of the aorta and other arteries were also found to increase with age, contributing to the tortuosity and thus to the increased lumen volume of these vessels frequently observed in arteriograms of old patients. Enlargement and stiffening are predominant in elastic arteries,32 ie, in large conduit arteries responsible for the cushioning function of the arterial system. The combination of arterial wall stiffening and increased arterial volume (enlargement + tortuosity) results in a smaller than expected decrease in total systemic arterial compliance.

As shown in *Figure 9* of Lakatta’s lead article in this issue, the arterial compliance index (pulse pressure [PP]/stroke volume index [SVI]), which reflects total systemic arterial compliance (related both to stiffness and volume), is less affected by aging than PWV (which reflects arterial wall stiffness itself). Thus, we may consider that the dramatic increase in pulse pressure in the elderly helps preserve systolic volume storage during ventricular ejection and thus diastolic blood runoff from the large arteries despite their reduced compliance. Therefore, the combination of arterial enlargement and increased central pulse pressure in the elderly can be considered as an incomplete compensatory mechanism for arterial stiffening due to aging.

**Arterial remodeling: adaptation to physical forces?**

Blood vessels are permanently subjected to mechanical stretching. As a result, due to the pulsatile nature of blood pressure and flow, the vessels are exposed to cyclic mechanical strain and shear stress. Blood pressure is the major determinant of vessel stretching. It creates radial and tangential forces that counteract the effects of intraluminal pressure and affect all cell types in the vessel. In contrast, fluid shear stress results from the friction of blood against the vessel wall, and it acts parallel to the vessel surface. Accordingly, shear stress principally affects the endothelial cells, which are strategically located at the blood and vessel wall interface. Alterations in stretch or shear stress invariably produce transformations in the vessel wall that aim to accommodate the new conditions and, ultimately, restore basal levels of tensile stress and shear stress.46,47 Hence, while acute changes in stretch or shear stress result in transient adjustments in vessel diameter, which are mediated through release of vasoactive agonists or change in myogenic tone, chronic alterations in mechanical forces usually result in important adaptive alterations of vessel wall shape and composition. “Vascular remodeling” designates those transformations that occur in vessels subjected mechanical stresses.

**Mechanical forces**

The blood pressure exerts forces perpendicular to the intraluminal surface of the vessel wall. These forces are balanced by intraparietal tangential forces in the longitudinal and circumferential directions exerted by the different components of the vessel wall, which oppose the distending effects of blood pressure in the circumferential direction. The force per unit length of vessel (pial tension) is related to the blood pressure (P) and the vessel radius (r) by Laplace’s law:

\[ T = P \cdot r \] [mm Hg·mm]

The relationship between circumferential tension and deformation of the vessel as intraluminal pressure increases depends both on the geometry of the vessel and the elastic characteristics of its wall. Circumferential tension is borne by the entire thickness of the arterial wall. Each component of the wall bears only part of this tension. The tension per unit of thickness represents the stress exerted on the wall in the circumferential direction. This is expressed as:

\[ \sigma = \frac{P \cdot r}{h} \] [mm Hg]

where h is the thickness of the wall.

**Wall stress and vascular remodeling in aging**

Numerous studies have demonstrated a direct relationship between the circumferential stress to which the vessel wall is exposed and the structure of the wall itself. When circumferential stress increases (as a result of an increase in arterial pressure), SMC hypertrophy and
increase in collagen and elastin contents ensue. Conversely, when circumferential stress decreases, the wall undergoes atrophy. For the sake of simplification, we can assume that everything occurs as though arterial thickness (the denominator of the equation determining tensile stress $\sigma = Pr/h$), increases in such a way as to balance out the increase in the numerator (wall tension), whether the latter is due to an increase in pressure or an increase in the radius of the vessel.

**Effects of radius changes**
The effects of mechanical tensile stress on the arterial wall have been extensively described and applied to the understanding of hypertension (Figure 2). Tensile stress is a powerful determinant of vascular structure, among other factors including sympathetic activity and autocrine and paracrine factors, especially the renin-angiotensin system. In elastic and large conduit arteries, the adaptive response to hypertension acts to reduce and eventually normalize tensile stress.

According to Laplace’s law, tensile stress can be modified by changes in lumen size and/or vascular wall thickness. In humans and animals, a consistent enlargement of the arteries is observed with increasing age. It is noteworthy that arteries continue to grow during the entire life, even after body size has stopped evolving. Aortic circumference increases with age, whatever the segment, from the ascending aortic arch to the bifurcation of the abdominal aorta. Age appears to have only a minimal effect on medial thickness. In contrast, the increase in intimal thickness with age is the main factor responsible for the well-known age-related increase in total wall thickness of the aorta. Interestingly, the changes in lumen radius and total wall thickness (media + intima) related to age are in agreement with the concept that tensile wall stress is maintained at an ideal value during the entire life under nonpathological conditions.

**Endothelial dysfunction and possible compensatory mechanisms**
Arterial vasodilation is undoubtedly impaired in the elderly. Most experimental and clinical studies suggest that NO production and/or access to smooth muscle are reduced in this population. However, some experimental studies in rat aorta reported a 7-fold increase with aging in the percentage of endothelial cells expressing NO synthase. Aging was found to be associated with a reduced ability of the endothelium to counteract contractile responses to endothelin and a reduced SMC responsiveness to this vasoconstrictor. This phenomenon could be understood as a limited compensation or adaptation to degenerative processes.

**CONCLUSION**
During aging, the arterial wall is subjected to physiological degenerative processes involving the endothelium, SMCs, and the extracellular matrix. These processes are accompanied by compensatory mechanisms that limit the consequences of degeneration. Most of the known compensatory mechanisms enhance the mechanical self-regulation of the arterial wall. The blood vessels possess humoral autocrine and paracrine mechanisms that enable them to react immediately to local hemodynamic changes, such as circumferential mechanical stress (which increases with pressure) and shear stress (which increases with blood flow). The immediate changes in local vasomotor...
tone provoked by these changes tend in most cases to normalize the vessel hemodynamics. If the alterations in local geometry induced by changes in vasomotor tone are inadequate to compensate for the changes in mechanical stress, the phenotype of the vascular cells may be modified and give rise to local trophic changes. These changes, tend, over the longer term, to restore the mechanical stresses to physiological levels. With purely local mechanisms, blood vessels are capable of true self-regulation, enabling them to adapt to their mechanical environment. The transduction mechanisms between mechanical and biochemical or endocrine signals are beginning to be better understood. Integrins, located at the cell surface, are likely to be key mechanosensors. Ion channels and other unknown stretch receptors presumably transduce the mechanical signal. As a result, several intracellular signaling pathways are activated including the tyrosine kinase c-Src, focal adhesion kinase (FAK), and the mitogen-activated protein (MAP)–activated MAP cascade, as well as the renin-angiotensin system. This opens up the exciting perspectives for therapies able to delay the degenerative processes and help the vascular system offset the alterations occurring with aging.

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Atrial fibrillation—a major health problem, particularly among the elderly—is associated with an increased risk of stroke, death, and heart failure. Yet, despite more than 120 years of research, the detailed molecular, cellular, and pathophysiological mechanisms remain poorly understood. The major recent advance in the management of these patients has come from clinical trials, which have identified age >65 y, history of hypertension, stroke, diabetes, and poor ventricular function as factors that independently predict an increased risk of stroke. Thus, patients >75 y with or without risk factors or patients <75 y with a single risk factor derive benefit from anticoagulation with warfarin, with good blood pressure control. The remaining patients have a low risk of stroke on aspirin, 325 mg/day. Consideration should always be given to cardioversion and maintaining sinus rhythm.

In Western societies, patients with atrial fibrillation (AF) are most often the elderly and not uncommonly women. AF is the most common arrhythmia found in adults,1-3 and it is twice as common as all other arrhythmias combined. There are an estimated 2.2 million people in the United States with AF.4 In developed countries, the prevalence of AF increases rapidly with age. The median age of patients with AF is approximately 75 years.5 In the >70-year age-group, the estimated prevalence of AF is 9%.5 In a community-based, Minnesota study, 16.1% of men and 12.2% of women >75 years of age had AF.6 A British study of patients examined in a general practice setting was consistent with the above.7 While the prevalence of AF is slightly higher in men, the absolute number of women and men with AF is approximately equal because there are more women than men in the older age-group.3

In addition to causing hemodynamic compromise, AF is a significant marker for higher incidences of stroke and increased mortality. In the Framingham heart study, the risk of stroke was 5.6 times greater in patients with AF than in comparably aged patients in sinus rhythm, and the risk increased from 1.5% in the 50- to 59-year age-group to 23.5% in the 80- to 89-year age-group.3 The risk of stroke seems independent of whether AF is constant or intermittent.5 Definitive clinical trials have shown that in selected patients protection from stroke using warfarin and to a lesser extent aspirin is highly effective.8

**ATRIAL FIBRILLATION AS AN ELECTROPHYSIOLOGY PROBLEM**

It has been more than 120 years since AF was first described.9 This fascinating arrhythmia continues to defy a fundamental understanding. In this section, we provide a brief, and therefore incomplete, review of recent advances in AF-related research from the bench to the organ systems level. We focus on those advances that have contributed to our understanding of the mechanisms of initiation, perpetuation (maintenance), and termination of AF.

As regards initiation and maintenance, there is general agreement that AF is most likely a reentrant rhythm disturbance.10 However, the precise pathophysiological bases for its initiation and maintenance have not been resolved. In addition, as newer and more sophisticated tools for the study of AF in experimental animals and in humans have become available, controversies such as whether AF results from focal or multiple reentrant mechanisms, or both, have reemerged.11

**Keywords:** arrhythmia; atrial fibrillation; elderly patient; genetics; anticoagulation; warfarin; aspirin; cardioversion

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In the original description of the multiple wavelet hypothesis of AF, as put forward by Moe et al.12 and later substantiated by Allessie et al.13 wavelets were thought to propagate randomly throughout the atria. However, more recent studies14,15 that have applied high-resolution mapping of wave propagation in both the time and frequency domains provide evidence that AF is not random,15 but is accompanied by a high degree of spatiotemporal periodicity. This has led to the hypothesis that maintenance of AF may depend on the uninterrupted periodic activity of a small number of discrete reentrant sites, established by the interaction of propagating waves with anatomical heterogeneities in the atria.16 It has also been proposed that the rapidly successive wave fronts emanating from these sources propagate through both atria and interact with anatomical and/or functional obstacles, leading to fragmentation and wavelet formation.16 In support of this idea is the observation in humans, which suggests that, in some patients, a single, repetitive focal source of activity propagates from an individual pulmonary vein to the remainder of the atrium as fibrillatory waves.17,18

In this regard, advances have occurred in the understanding of geometrical factors, such as wave front curvature19 and sink-source relationships at areas of tissue expansion,20 and in the application of nonlinear dynamics theory to the spatial and temporal organization underlying complex cardiac arrhythmias,21 particularly during ventricular fibrillation. Such advances may be relevant to the ultimate understanding of the mechanisms of initiation of AF by the interaction of the propagating wave fronts with anatomic or functional obstacles in their paths.13 Bioinformatics may provide analysis and modeling tools for research aimed at the study of the manner in which electrical “fibrillatory” waves interact with the highly complex three-dimensional structure of the atria.13,21

Exciting new information has become available about genetic abnormalities leading or predisposing to AF. Brugada et al.22 reported three families with inherited AF with a locus on chromosomal region 10q.22,23 More recently, Roberts23 found that several other kindreds with AF also linked to the same markers. It remains to be established what is the percentage of patients with AF who have genetic defects. How genetics impacts upon the aging process is not known.

**ATRIAL FIBRILLATION AS A MANIFESTATION OF THE AGING PROCESS**

Attributing a condition to the aging process is always difficult because it is often impossible to separate physiological aging from the development of comorbid disease. There have been carefully conducted studies of the aging cardiovascular system.24 A diligent attempt has been made to screen for latent coronary and other cardiovascular diseases. It is most likely that the increasing prevalence and higher incidence of atrial arrhythmias, including AF, Abnormalities of the conduction system have been reported in apparently healthy volunteers with the consistent finding of a prolongation of the PR interval and a higher prevalence of first-degree atrioventricular block.25,26 In addition, unexplained sinus node abnormalities in apparently healthy nonathletic older individuals have been observed.29 Exercise-induced ventricular arrhythmias have been associated with the development of spontaneous AF and supraventricular tachycardia.27

It is most likely that the increasing prevalence of AF with age is due to the influence of comorbid disease affecting a myocardium predisposed to AF. It is therefore of critical importance that diligent control of blood pressure is achieved, thereby reducing hypertrophy, which can result in diastolic dysfunction and left atrial enlargement. In addition, appropriate pharmacologic and more aggressive treatment of conditions such as mitral valve disease, which may also predispose to an enlarged left atrium, should lower the incidence with advancing age. The avoidance of certain drugs such as digoxin, bronchial dilators, tricyclic antidepressants, and caffeine-containing foods may also reduce the incidence in the elderly. Thyrotoxicosis is often present in the elderly without the usual clinical manifestations and is an important reversible cause of AF. Attention to electrolyte imbalance,
especially with diuretic therapy, may also reduce the incidence of AF in the elderly.

STROKE PREVENTION
Among patients over the age of 75, the prevalence of AF is about 15%. Stroke is the most important complication in this age-group, robbing the elderly of their dignity and often resulting in significant morbidity, and may lead to heart failure and death. The pivotal clinical question is to determine which patients would benefit from anticoagulation using warfarin and which patients from aspirin for prophylaxis against stroke. Guidance is provided by eight large prospective clinical trials. The first five trials were primary stroke prevention, placebo-controlled, prospective, randomized trials. The Stroke Prevention in Atrial Fibrillation–II (SPAF II) trial compared aspirin and warfarin and the European AF trial was directed at secondary prevention. There was a single trial evaluating warfarin and aspirin in combination. These trials found that the elderly, simply by virtue of their age, automatically fall into a high-risk group with respect to the occurrence of stroke. Patients of any age who have a history of high blood pressure, diabetes, a previous transient ischemic attack or stroke, or poor ventricular function also qualify as high risk. Thus, among the elderly, the annual risk of stroke, untreated, can vary from 4% to 12% and above. It is among these patients that the risk of stroke is not substantially reduced by aspirin. Of critical importance, therefore, is to consider anticoagulation in this group of patients. The SPAF III study found that the risk of stroke, using international normalized ratio (INR)-adjusted warfarin in high-risk patients was 1.7 per year, a substantial reduction over the risk reduction achieved by aspirin and a subtherapeutic dose of warfarin when used in combination. Physicians tend to use anticoagulation cautiously in the elderly because of the perceived risk of major bleeding, particularly intracerebral bleeding. However, the data would suggest that if the INR is maintained within a range of 2.0-3.0 and the blood pressure is controlled, the risk of intracerebral and major life-threatening bleeds can be quite low and is far outweighed by the benefit of anticoagulant therapy. Minor bleeding is always more common in the anticoagulated patient. These non–life-threatening minor bleeds might unmask early malignancies, common in this patient population, which might not ordinarily be detected if it were not for the stress of anticoagulation. While this is not a proven cost-effective strategy, it is probably prudent to evaluate all anticoagulation-induced bleedings aggressively, particularly if they occur in the elderly, and particularly if they are a new finding.

CARDIOVERSION VERSUS RATE CONTROL AND STROKE PREVENTION
There is an ongoing and unresolved debate concerning the wisdom of cardioverting patients with AF and maintaining them in sinus rhythm. The essence of the debate is centered around the success of cardioversion and the success of maintaining sinus rhythm in the long term and the side effects of the drugs that are used for this purpose. Definitive data concerning the success of cardioversion and maintenance of sinus rhythm are not available and are being collected in the SAFETY and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trials, which are ongoing. It is estimated that taking the best case, only about 50% of patients successfully cardioverted remain in sinus rhythm 12 months after the cardioversion. In addition, many of the drugs that are used to maintain patients in sinus rhythm have important side effects that preclude their use. A commonly used medication in this setting is amiodarone. Even at low dose, it may be associated with hypothyroidism and hyperthyroidism, as well as pulmonary fibrosis, hepatic dysfunction, and skin sensitivity to sunlight. Sotalol, another drug commonly used to maintain sinus rhythm, is associated with prolongation of the QT interval, risk of ventricular tachycardia, and typical problems associated with all β-blockers, which are brachycardia, asthma, and deterioration of ventricular function. Propafenone and mexiletine should only be used in patients who have normal ventricular function and who do not have overt coronary disease because of risk of proarrhythmia. Dofetilide also carries a risk of QT prolongation and proarrhythmia. Among the elderly, AF is often associated with a more generalized conduction system disease. Drugs such as sotalol and amiodarone may induce significant brachycardia, particularly when used in association with other agents that block the atrioventricular node. In these patients, the use of a backup pacemaker may be indicated.

The counterargument supports the use of cardioversion, particularly early cardioversion, and is based on the work of Allessie et al in goats. They demonstrated that AF begets AF because of the development of irreversible changes to the atrial wall. Extrapolating these data to humans, it appears that early cardioversion is more likely to be successful in the long term than cardioversion in patients that have had AF for a long period of time.
The approach of rate control and stroke prevention is therefore a viable alternative, particularly if the AF is well tolerated clinically, which is often the case in the elderly. This approach is limited by the difficulty in using warfarin because of its many interactions with food and other pharmacological agents, as well as the fear of using warfarin in an elderly population.

AGGRESSIVE MANAGEMENT STRATEGIES

In a minority of patients, particularly those elderly that remain asymptomatic, a more aggressive approach may be needed. Ablation of the atrioventricular node with pacing improves hemodynamics and symptoms. More recently, implantable left atrial defibrillators have been developed and are under evaluation.

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Myocardium that has been exposed to a brief episode or several episodes of ischemia and reperfusion exhibits a strange and unexpected change in its biology. Unlikely as it may seem, this exposure protects it against the deleterious effects of a prolonged episode of ischemia.

**PRECONDITIONING AND CARDIOPROTECTION**

In fact, myocardium that has been treated in this way will survive a test episode of ischemia that is sufficiently severe to kill most of the ischemic myocytes in virgin heart. This protective effect is called *preconditioning with ischemia* and is the strongest protective effect so far identified in the treatment of regional ischemia in vivo.

Preconditioning does not prevent myocyte death. Rather, preconditioning allows myocytes to survive in an ischemic state for a longer period of time than virgin myocytes; thus, it delays, but does not prevent myocyte death. In addition, the protection afforded by preconditioning is transient. In the dog heart, the species in which the phenomenon was discovered, the protection is about half gone after 120 minutes and is dissipated totally by 180 minutes of reperfusion. However, if the heart is exposed to a second preconditioning episode of ischemia and reperfusion, cardioprotection can be reinstated.

**PRECONDITIONING AND THE HUMAN HEART**

There are three lines of indirect evidence supporting the premise that the human heart can also be preconditioned with ischemia.

- The first is intuitive and is the fact that all mammalian hearts so far tested including dogs, pigs, rats, rabbits, and ponies can be preconditioned. The human heart should be no exception to what most investigators assume is a general response of the mammalian heart to ischemia.
- The second is the fact that responses similar to those seen in preconditioned animal hearts are seen in the human heart when brief periods of ischemia and reperfusion are given to patients undergoing cardiac catheterization prior to angioplasty. In such patients, 2 minutes of ischemia followed by reperfusion greatly alters the response of the heart to a second episode of ischemia. Moreover, during the second 2-minute episode of ischemia, the preconditioned bed exhibits the same responses to a test episode of ischemia as those seen in the preconditioned animal heart, including a reduction both in the degree of ST-segment elevation and in the magnitude of lactate release compared with the changes seen in the initial preconditioning episode of ischemia.

Finally, repetitive episodes of angina probably precondition the human heart. The best evidence for this belief comes from the Thrombolysis In Myocardial Infarction (TIMI) 4 trial in which the group of patients that exhibited angina prior to developing myocardial infarction, i.e., the presumed preconditioned group, did better than the group that was free of angina.

**MOLECULAR MECHANISM OF PRECONDITIONING**

It is of interest that the molecular mechanism of preconditioning with ischemia is probably related to the degradation of the adenine nucleotide pool that occurs during ischemia.
Destruction of the pool is associated with the release of adenosine from the ischemic myocytes. Significant adenosine production begins after 10 to 20 seconds of ischemia, ie, shortly after the myocardium converts to anaerobic glycolysis as its chief source of energy. Since energy release during anaerobic metabolism is limited, adenosine diphosphate (ADP), which still has one high-energy phosphate bond, accumulates. The high-energy phosphate bond of ADP is salvaged by a reaction (adenylate kinase) that produces an excess of intracellular adenosine monophosphate (AMP), which is degraded into adenosine. Unlike AMP, adenosine can exit from the myocyte to the extracellular space, where it stimulates myocyte A₁ receptors. These receptors induce a complex set of intracellular signaling reactions that somehow lead to cardioprotection. These intracellular signaling reactions involve activation of a variety of protein kinases, especially protein kinase C. When active, these kinases phosphorylate proteins, including enzymes and ion channels with resultant changes in activity. However, it is not clear how these phosphorylations lead to protection.

**PRECONDITIONING AS A THERAPEUTIC TOOL**

Because the preconditioning effect is transient, it is unlikely that preconditioning with ischemia itself will be useful as a therapeutic tool in patients with severe coronary artery disease because the sequential episodes of ischemia that would be required to maintain the preconditioned state eventually would induce deleterious effects in the treated myocardium. The main negative effect would be depletion of the adenine nucleotide pool. The depletion would occur because some of the pool is lost with each episode of ischemia and because adenine nucleotide pool resynthesis is very slow in healthy heart tissue. This negative view about the maintenance of the preconditioned state with repetitive episodes of ischemia and reperfusion is based on experimental studies using maximal preconditioning stimuli. Lesser degrees of ischemia such as those seen in angina also precondition, and probably do not result in depletion of the adenine nucleotide pool. However, this idea remains untested. Finally, the use of a single episode of ischemia to precondition may prove useful, eg, to improve the tolerance of the heart to ischemia in patients on pump bypass for cardiac surgery. Here, the aim would be to keep as many of the ischemic myocytes alive during bypass as possible and also to improve their function when coronary flow is restored.

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**PERSPECTIVES**

The important aspect of the above, aside from its intellectual interest, is the possibility that one could develop a drug that would maintain the myocardium of a patient with severe coronary disease in a continuous preconditioned state. The advantage would be increased tolerance to ischemia and a longer time available to intervene if such a patient obstructed a major branch of a coronary artery. Several drugs in the early phase of development have been shown experimentally to be cardioprotective, in fact as protective against infarction as is preconditioning with ischemia. Thus, there is reason to hope that a safe cardioprotective pharmacological agent will be developed.
Cardiovascular Aging

Summaries of Ten Seminal Papers

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8. Intracellular calcium transients and developed tension in rat heart muscle. A mechanism for the negative interval–strength relationship
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9. Age-associated changes in beta-adrenergic modulation on rat cardiac excitation–contraction coupling

10. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women
J. L. Fleg and others. J Appl Physiol. 1995

Selection of seminal papers by E. G. Lakatta, MD
Laboratory of Cardiovascular Science - Gerontology Research Center - National Institute on Aging - Intramural Research Program - NIH - Baltimore - Md - USA

Highlights of the years by
Ian Mudway, MD
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Experimental studies of physical fitness in relation to age

S. Robinson

Arbeitsphysiologie. 1938;10:251-323

Although it was well recognized that older individuals have reduced exercise tolerance, this exhaustive work from the Harvard Fatigue Laboratory quantitatively sorted out the relative contributions of the cardiac, pulmonary, and hematological systems. Nestled amidst the pages of a German physiology journal, this 70-page tour de force (in English) actually makes for an interesting read on a rainy Sunday. Much of what we practice and preach today regarding exercise performance is rooted in this extensive report of physiological variables, recorded at rest and during treadmill exercise. The strengths of this work are the age range of the participants (6 to 91 years) and the completeness of the data collection.

Ninety-three males, who did not engage in athletics regularly, were subjected to measurements of heart rate (HR), blood pressure, lung parameters by spirometry, arterial blood gas, venous lactic acid, and oxygen utilization at rest and during two levels of exertion—minimal and exhaustive. For illustrative purposes, the subjects were separated into 12 age-groups including middle-class boys, "inmates of an orphanage," preparatory school and college students, and Harvard faculty.

At rest, HR did not change with age, although increasing age was related to decreased HR variability. Basal HR was positively correlated with the maximal HR achieved during exertion. Resting metabolic rate, measured as oxygen uptake per body surface area, declined precipitously with age until age 30, leveled off, and declined again after age 60. Age did not influence resting alveolar P_O2 and P_Co2, but lung vital capacity is decreased with age.

As predicted, maximal work and oxygen consumption decreased with increasing age. Peak exercise HR was also blunted with age as was the slope of HR decline in recovery. Despite the decrease in cardioacceleration, older men were more efficient at extracting oxygen as confirmed by increased blood lactic acid levels. Older men also had more efficient alveolar ventilation during exercise compared with the youngsters. This adaptation, coupled with an increased respiratory quotient (a surrogate measure of carbohydrate utilization), leads to a more economical energy transfer during exercise. In contrast to this increased efficiency in older men, younger boys, who seem unbothered by spurts of activity, had lower lactic acid levels, implying a decreased capacity to deliver oxygen to tissues despite higher HRs during activity.

Robinson also noted an age-related difference in the adaptive nature of the cardiovascular system during stress. Whereas rapid adjustments of respiratory rate, oxygen intake, and directional shunting of blood occur in the young, these stress-induced adaptations take longer in older adults. This implies a greater reliance on the autonomic nervous system during moderate work in younger boys.

In summary, this work addresses the heart of the matter of the limited exercise tolerance in the elderly by identifying the central role of age-related physiological changes in the cardiovascular system. In 1870, Adolph Fick noted that oxygen consumption is directly related to the flow of blood (HR x stroke volume) and indirectly to oxygen extraction by the tissues. Robinson’s work provides evidence that the diminished maximal HR with age is paramount in reducing oxygen consumption during exercise, a seminal observation that has stood the test of time.

1938

George and Ladislav Biro invent the ball-point pen;
Hitler marches into Austria proclaiming political and geographical union with Germany;
and Orson Wells broadcasts his adaptation of H. G. Wells’s “War of the Worlds,” creating a nationwide panic as listeners believe that aliens have landed in New Jersey.
While age-associated changes in physiology were being studied in a variety of species, Albert et al set out to explore both possible biochemical and mechanical alterations at the myocyte level. The goal of these experiments was to investigate the relationship between a biochemical property (ATPase activity) and the mechanics of contraction. Since prior work had suggested an age-related diminution in ATPase activity, myocytes of rats of various ages were used to gain insight into the influence of this biochemical alteration on myocardial contraction. Thus, although the aging process was actually exploited as an experimental condition, seminal observations were revealed about myocyte aging: a prolonged contraction duration with preserved contractile force.

The experimental design used by Alpert and coworkers was relatively simple: they measured ATPase activity in myofibrils isolated from hearts of Simonsen rats of various ages (100 to 1000 days old) in response to increasing concentrations of calcium. To correlate this biochemical measurement to the mechanical properties of the myocytes, force velocity, length tension, series and parallel elasticity, and time to peak tension and half relaxation were recorded in cells of the same hearts.

Myofibrillar ATPase activity increased with escalating calcium levels regardless myocyte age. The dependence of ATPase activity on calcium exists even when myofibrils are extracted with glycerol, implying a relationship that is independent of a membrane property. Although age did not affect the relationship between myofibrillar ATPase activity and calcium concentration, the overall ATPase activity was decreased by 14% in myocytes from the old compared with the young hearts.

The influence of age on the mechanical properties of the myocytes was surprising in these experiments. Age did not affect the amplitude of the contraction or the length-tension relationship, but interestingly, the shortening velocity was decreased as a function of increasing rat age. This relationship held true regardless of the initial load.

Thus, although the contractile force in older cells is as intense as in younger myocytes, the contraction develops more slowly and lasts longer in older cells. Moreover, the correlation between the diminished myofibrillar ATPase activity and a prolonged contraction duration suggests a possible biochemical explanation for this mechanical alteration.

Given the experimental design, definitive conclusions regarding a cause-effect relationship between ATPase activity and prolonged myocardial contraction in aging could not be drawn. On a cellular level, the observation of a powerful, but slower, contraction in older myocytes raises the possible role of an age-related alteration in intracellular calcium cycling, perhaps by the sarcoplasmic reticulum, in these mechanical changes. The unchanged amplitude of contractile force in aged myocytes suggests either an alteration in calcium timing and/or superimposed stiffness. Regardless of the mechanism, this important characteristic of cardiovascular aging, prolonged contraction and therefore relaxation, is consistent across a multitude of species and has important clinical implications. A delay in early diastolic left ventricular filling may lead to symptoms of dyspnea, angina, and lightheadedness when an older individual is faced with a tachycardic stress.

Christian Barnard performs the world’s first successful heart transplant, but the patient dies 18 days later; Jerome Friedman, Henry Kendall, and Richard Taylor discover that protons and neutrons are composed of even smaller particles called quarks; and a right-wing military coup deposes King Constantine II of Greece.
Reduction in maximal oxygen uptake with age

I. Astrand, P. O. Astrand, I. Hallback, A. Kilbom


One of the greatest challenges in the field of aging research is to distinguish those physiologic changes that are due to normal aging from those changes influenced by lifestyle, disease, diet, exercise, and environmental factors. Another potential confounder of gerontological studies is the birth-cohort effect. Cross-sectional studies, which consist of a single measurement in time of individuals of various ages, are particularly subject to these shortcomings. Yet, because they are simple, economical, and efficient to perform, cross-sectional studies provide the majority of our early understanding of physiological changes associated with aging. Longitudinally collected data, obtained by repeated measurements of the same variables in the same subjects over time, can overcome some of the limitations of cross-sectional data.

In an effort to alleviate concern that prior studies reporting an age-related decline in oxygen consumption with exercise were tainted by their cross-sectional design, two Swedish exercise physiologists, the Astrands, reported longitudinal changes in exercise parameters by collecting data from Swedish gym teachers who had been studied 21 years earlier. Forty-four female and 42 male physical education students initially performed submaximal and maximal exercise on a bicycle ergometer and treadmill in 1949. In 1970, the investigators tracked down 35 and 31 of the original women and men, respectively, to undergo similar exercise testing. It is noteworthy that since subjects were involved in teaching physical fitness, most exercised regularly over the 20 years and remained svelte.

With each subject serving as his or her own control, longitudinal changes in cardiopulmonary parameters were described. Although some technical differences exist between the 1949 and 1970 data collection, the novelty of these longitudinal data persists. In 1949, the average age of the female and male subjects was 22 and 26 years, respectively. Over the 21 years, women gained about 2.5 kilograms, whereas men lost about the same amount. Regarding lung function, vital capacity did not change over time, but residual volume decreased suggesting a longitudinal increase in total lung capacity. Consistent with cross-sectional data, maximal oxygen uptake, measured by a Douglas bag, decreased over time by 22% in women and 20% in men. This decrease was not influenced by changes in weight. Also demonstrated in numerous cross-sectional studies, an age-associated decrease in cardioacceleration during exercise was confirmed by these longitudinal data.

In this group of health-conscious athletes, a decrease in maximum oxygen consumption underscores a true age-associated physiological change rather than a decrease in overall activity over time. Although it is possible to raise oxygen consumption by a brief exercise program, it is unlikely that such consistent findings could be explained by a quick “buffing up” period just before the 1970 testing. When considering the candidate changes that may impact the decrease in oxygen consumption, prior cross-sectional studies pointed to the decrease in maximal heart rate with exercise. However, in this longitudinal study, the discrepancy between a 7% decrease in cardioacceleration and a 20% decrease in oxygen consumption raises the possibility of an additional age-associated diminution in stroke volume and/or tissue oxygen extraction. An increase in lactic acid content in 1970 may suggest the latter.
Diminished inotropic response of aged myocardium to catecholamines

Circ Res. 1975;36:262-269

Independent laboratory work and clinical observations in humans and animals consistently report a decrease in the cardiovascular responsiveness to stress with increasing age. Specifically, diminished maximal heart rate, decreased peripheral vasodilation, and dampened myocardial contractility to stress raised concern of altered catecholamine production and/or response. Similar physiologic changes in younger subjects after β-blockade further supported an adrenergically-mediated alteration. Lakatta et al address possible mechanisms underlying the age-related decrease in cardiovascular performance to β-adrenergic stimulation (βAS) in this elegant series of experiments on isolated rat heart muscle. By using isolated myocardium, the investigators established that the blunted inotropic stress response with age was due to “intrinsic” changes in the myocytes rather than to a defect in the elaboration of catecholamines.

Left ventricular trabeculae carnae muscle preparations were isolated from young adult (6 months old), middle-aged (12 months old), and old (25 months old) Wistar rats. Contractile parameters of the heart muscles were measured at baseline and in response to increasing concentrations of norepinephrine (NE). Similar measurements were made at differing calcium concentrations to tease out the role of calcium availability in catecholamine response.

Basal resting tension, active tension (AT), and maximal rate of tension development (dT/dt) were unchanged with age. However, as previously described in vitro (see Alpert et al summary) and in vivo, contraction duration in the oldest muscle was 17% and 19% longer than in the muscle of young adult and middle-aged rats, respectively (P<0.001).

Increased concentrations of NE lead to increased dT/dt, AT, and contraction duration shortening. Despite the consistency of these general responses to βAS, significant age-dependent differences were seen. Specifically, dT/dt to the highest dose of NE was twofold greater in the youngest compared with the oldest muscle (P<0.001). Whereas AT increased to NE in young and middle-aged muscle, it remained constant in the oldest tissue. Similarly, contraction duration shortening to the highest concentrations of NE was less robust in the oldest myocardium. By demonstrating similar age effects with NE and isoproterenol (which has higher receptor affinity and is negligibly taken up by storage sites), the investigators demonstrate that the diminished inotropic response with increasing age is unlikely related to altered β-adrenergic receptor affinity or storage site uptake.

In contrast to the blunted response to catecholamines in aged myocardium, there is no age difference in the increase in dT/dt or AT to increasing concentrations of calcium. This finding supports that the aged myofilament apparatus and its contractile ability are intact when calcium is abundant. The catecholamine-induced increase in contractile force and twitch duration shortening are governed by calcium presence at the contractile protein site. Thus, the blunted inotropic response to βAS may be explained by an inability of catecholamines to liberate intracellular calcium to the degree needed for contraction.

By performing these experiments on three age-groups, thereby providing dose-response curves, the authors confirm that the inotropic response to βAS is blunted with age. Moreover, they provide evidence supporting an alteration intrinsic to the aging myocyte that may be due to calcium cycling.

Manuel Orantes and Chris Evert win the US open tennis championships (for men and women, respectively); Pol Pot and the Khmer Rouge take over Cambodia; and John W. Comforth (Australia) and Vladimir Prelog (Switzerland) are awarded chemistry Nobel Prize for research on structure of antibiotics and cholesterol.
In the mid 1950s, Sir W. Pickering, in referring to the similarities between long-standing hypertension and aging, likened aging to “muted hypertension” and hypertension to “accelerated aging.” This statement is supported by both clinical and experimental observations, including cardiac hypertrophy, a prolonged rate of contraction, normal baseline contractile function, in both circumstances. Animal models of hypertension, such as aortic banding, were established to gain further insight into the possible similarities between these two conditions. In this series of experiments, Meerson and colleagues compare and contrast the myocardial effects of hypertension and aging at the molecular level.

To address their hypothesis that aging and hypertension manifest as alterations in the myocardial balance of protein synthesis and degradation, the investigators measured RNA concentration, the rate of RNA and protein synthesis, and efficiency of protein translation in myocardium from three groups of rats. One experimental group of rats were aged (23 months old) while the hypertensive group consisted of 11-month-old rats that had undergone 6 months of abdominal aortic banding. Three- to 4-month-old non-hypertensive rats served as the reference group.

The absolute mass of the hearts of the hypertensive rats increased by 31% in comparison with control adult rats, with a significant increase in the heart weight-to-body weight ratio. The hearts of older rats also increased in weight, but the heart weight-to-body weight ratio was similar to that of younger control rats. A 20% decline in myocardial RNA concentration was noted in both aged and hypertensive myocardium compared with younger animals. While the rate of RNA synthesis was also depressed in aged and hypertensive myocardium, the latter was decreased by an additional 25% more than the former. Diminished transcriptional levels caused by a fall in RNA degradation led to a decreased ribosome content in the myocytes and thus the decreased RNA concentration. In vitro and in vivo evidence is provided that myocardial protein synthesis and degradation rates are similarly depressed in hypertension and aging. A reduction in the numbers of ribosomes and an altered ability to synthesize proteins are thought to contribute to the 46% decrease in protein synthesis seen in both aged and hypertensive myocardium. Deficiencies in transfer RNA (tRNA) may decrease the translational rates and also contribute to the decrease in protein synthesis. Thus, a loss in capacity for RNA and protein turnover and renewal of ribosomes leads to an accumulation of “defective” macromolecules in the myocytes.

The authors conclude that, because of similar changes in the myocyte at the molecular level including a decrease in synthesis and degradation of RNA and protein, hypertension serves as a model for cardiovascular aging. While cardiac hypertrophy due to aging and hypertension share some similarities at the molecular level, differences in these two conditions also exist. Aging is associated with hypertrophy of the right as well as the left ventricle, and the magnitude of this hypertrophy is far less than that which occurs in hypertensive models. In both cases, hypertrophy appears to be related to the increased afterload of stiffened vasculature. While the cumulative pathway of increased cell length and loading is similar in the two conditions, the commonality may lie upstream, as in a common messenger such as calcium (see Lakatta, Circulation, 1987;75(suppl I):I69, for review).

1978

Louise Brown, the first test-tube baby, is born at Oldham Hospital in London; Italian prime minister Aldo Moro is kidnapped and killed by left-wing terrorists; and Sony introduces the Walkman

F. Z. Meerson, M. P. Javich, M. I. Lerman

J Mol Cell Cardiol. 1978;10:145-159
A dilemma developed in how to apply the building body of evidence from laboratory studies regarding age-related cardiovascular changes to the clinical arena. Two obstacles prevented extrapolation from in vitro data to humans: the simplicity of the model and the jargon of contractility. Animal models consistently demonstrated prolonged baseline myocardial contractility and a blunted inotropic response to β-adrenergic stimulation with increasing aging. Moving from the test tube to the organism level is complicated by the inseparable interactions between preload, contractility, afterload, and autonomic control. Moreover, when describing myocardial function clinically, ejection fraction (EF) seems to serve as the universal language. All prior aging studies reported measures of contractility such as stroke volume, developed tension, or active tension. Although EF is not truly a measure of contractility, it is the currency of clinical and therapeutic decisionmaking. The time had come to bridge the aging rat data to the clinical realm. Implementing a new technology, radionuclide angiocardiography, Port et al set out to establish whether resting EF or peak exercise EF changed with age.

The subjects consisted of 77 healthy volunteers (31 women and 46 men), screened for known cardiovascular, pulmonary, renal disease, as well as hyperlipidemia, excessive smoking, diabetes, and hypertension. The participants, who ranged in age from 20 to 95 years, underwent upright bicycle ergometry, while EF was determined by first-pass radionuclide angiocardiography. This technique allows for the assessment of regional wall motion abnormalities (RWMAs).

Consistent with the results of Robinson 42 years before (see summary), resting heart rate (HR) did not change with age, but systolic blood pressure (BP) increased with age. Despite an increase in systolic BP, mean BP was unaltered with age, confirming another hallmark of cardiovascular aging—increased central arterial stiffness. No relationship between age and resting EF (mean±SD = 0.64±0.07) or left ventricular end-diastolic volume index (LVEDVI) was seen. Moreover, no RWMAs were detected at rest.

At peak cardiac workload, EF decreased with increasing age. While only 1 of the 48 subjects under age 60 had a peak EF<0.60, 13 of 29 subjects over age 60 had a peak EF<0.60. This finding supports an age-associated reduction in contractile reserve. An age-related change in LVEDVI did not account for the EF reduction. It is tempting to speculate that reduced HR accounts for declined EF. However, using linear regression, the authors conclude that failure to augment HR alone did not fully explain the dampened EF.

This study also gave birth to a realization of the magnitude of “silent” ischemia in the elderly. Although no subject experienced anginal symptoms during exercise, positive electrocardiographic changes consistent with ischemia were seen in 2 older subjects (66 and 74 years old). While no exercise-induced RWMAs were seen in subjects under age 50, they increased with age, such that 44% of subjects in their 8th through 10th decade developed RWMAs during exercise. This finding was reproduced by Fleg et al who report 30% of myocardial infarctions are “silent” in the elderly (Circulation, 1990,81:423).

The authors conclude that while resting EF does not vary with age, EF at peak exercise is reduced with increasing age. They speculate that while structural and biochemical alterations may contribute to these changes, the impact of silent ischemia must not be overlooked.

Effect of age on the response of the left ventricular ejection fraction to exercise

S. Port, F. R. Cobb, R. E. Coleman, R. H. Jones

Role of aortic input impedance in the decreased cardiovascular response to exercise with aging in dogs

F. C. Yin, M. L. Weisfeldt, W. R. Milnor


Around the same time Port and coworkers were pursuing the impact of age and myocardial contractile reserve on decreased exercise performance, Yin et al focused their attention on the possible contribution of increased afterload. Rather than the simplistic view that the vasculature acts in accordance to Ohm’s Law, these investigators sorted out the relative impact of steady (resistance) and pulsatile (characteristic impedance [CI]) loads imposed by the vasculature on the ejecting left ventricle both at rest and during exercise. Additionally, they sought to understand the influence of age on catecholamines. Their hypotheses were that with aging (i) increased vascular stiffness contributes to the decreased cardiac response to exercise and (ii) a decreased inotropic and chronotropic response to β-adrenergic stimulation (βAS) contributes to the blunted exercise performance. The experimental model employed in this study was novel: young and old dogs that were chronically instrumented with a probe that simultaneously measures blood flow and pressure. Recordings were made at rest and during a treadmill exercise, before and after pharmacological β-adrenergic blockade.

At rest, no difference was found between the seven 2-year-old and seven 10-year-old beagles in heart rate (HR), stroke volume (SV), cardiac output, aortic pressures, or impedance. In contrast, exercise elicited significant age-related differences in vascular and thus cardiac performance. A marked reduction in exercise tolerance was noted in old dogs, none of which completed the new trick of extreme exercise. At low levels of exercise, vascular resistance was decreased in both young and old dogs. Whereas this steady component of vascular impedance continued to fall during moderate and severe exercise in the young dogs, it remained constant during these higher exertional levels in the older dogs. Contributing more to the diminished SV attained by the older dogs during peak exercise, the pulsatile component of afterload, CI, increased by 20% during low levels of exercise and remained elevated during higher work levels. In contrast, CI dropped during exercise in the young dogs. Aortic acceleration, a measure influenced by both load and inotropy, remained constant throughout exercise, regardless of age. Therefore, increased load is implicated in the decreased inotropy at peak exercise levels in older dogs.

Catecholamines play an important role in the regulation of cardiovascular response to exercise by influencing inotropic, chronotropic, and vasodilatory response. Decreased responsiveness to βAS with aging plays an important role in the age-related changes in vascular load and inotropy during exercise. Blockade of β-adrenergic receptors with propranolol abolished the age-related differences in vascular loading during exertion. Specifically, CI increased during exercise in β-blocked younger dogs resulting in diminished SV.

In summary, an increase in pulsatile load during exercise appears to contribute to the diminished SV (and therefore cardiac output) achieved during exercise in older dogs. This component of afterload is largely influenced by changes in the size and structure of the proximal central vasculature. At higher levels of activity, decreased response to βAS also contributes to the increased vascular load and decreased exercise tolerance in older individuals.

Egyptian president Anwar el-Sadat is assassinated by Islamic extremists during a military parade in Cairo; Ronald Reagan and Pope John Paul II survive assassination attempts; and Prince Charles marries Lady Diana Spencer: the wedding has a worldwide television audience of over 700 million people. 

1981
Intracellular calcium transients and developed tension in rat heart muscle. A mechanism for the negative interval–strength relationship

C. H. Orchard, E. G. Lakatta

*J Gen Physiol.* 1985;86:637-651

One of the hallmarks of cardiovascular aging is prolonged myocyte contraction, which leads to delayed early diastolic filling. Speculation arose that a lengthened intracellular calcium (Ca\(^{2+}\)) transient could be responsible for this age-related change. In normal excitation-coupling, an initial depolarization causes Ca\(^{2+}\) influx through L-type sarcolemmal Ca\(^{2+}\) channels delivering Ca\(^{2+}\) to myofilaments for contraction. Calcium is then removed from the cytoplasm by sarcolemmal ATP-dependent Ca\(^{2+}\) pumps. These oscillations in intracellular Ca\(^{2+}\) currents require a certain amount of time for reconstitution. Given the complexity of Ca\(^{2+}\) cycling, there are numerous targets for possible age-associated alterations that may lead to a lengthened Ca\(^{2+}\) transient. This series of experiments by Orchard and Lakatta exploit the chemiluminescent jellyfish protein aequorin as a surrogate measure of cytoplasmic Ca\(^{2+}\) to explore the possible alterations in cycling that may prolong contraction.

The primary goal of this work was to establish the relationship between the intracellular Ca\(^{2+}\) transient and developed tension in response to varying rates of stimulation. A negative interval–strength relationship exists in rat myocardium such that increased stimulation frequency leads to decreased Ca\(^{2+}\) transient. This series of experiments by Orchard and Lakatta exploit the chemiluminescent jellyfish protein aequorin as a surrogate measure of cytoplasmic Ca\(^{2+}\) to explore the possible alterations in cycling that may prolong contraction.

The aequorin light transient, which reflects intracellular Ca\(^{2+}\) level, was closely correlated with peak tension of the papillary muscles \((r = 0.89)\). Similar amplitudes of aequorin light transients were seen in myocardium from 6-month-old and 24-month-old rats. However, despite these comparable levels of total intracellular Ca\(^{2+}\) and twitch force in old and young myocardium, both the time-to-peak tension and the half-time relaxation of developed tension were delayed in aged myocytes. The authors speculate that this prolonged tension and slower rate of relaxation may be due to slower sequestration of calcium by the sarcoplasmic reticulum (SR).

Consistent with previous studies on rat myocardium, increased stimulation rate was associated with decreased Ca\(^{2+}\) transient and decreased developed tension. This finding was consistent in both age-groups. However, when performed in a bath of increased Ca\(^{2+}\) concentration, the contractile response to increased stimulation frequency of young muscle was no longer diminished. In contrast to the ability of the young myocardium to overcome this negative interval–strength relationship when performed in the presence of higher Ca\(^{2+}\) concentrations, aged myocardium continued to respond to increased stimulation frequency with decreased intracellular Ca\(^{2+}\) transient and developed tension. The investigators conclude that the negative interval–strength relationship may be due to an age-associated alteration in the time-dependent repriming of the SR with Ca\(^{2+}\).

Coca-Cola attempts to alter its 99-year-old formula to attract younger drinkers: the new Cola grows and they return to the original product; Mikhail Gorbachev becomes the Soviet leader and instigates a broad range of reforms; and British scientists report the appearance of an enormous hole in the ozone layer over Antarctica.
Age-associated changes in beta-adrenergic modulation on rat cardiac excitation-contraction coupling

R. P. Xiao, H. A. Spurgeon, F. O'Connor, E. G. Lakatta

*J Clin Invest.* 1994;94:2051-2059

A ge-associated decrease in cardiovascular responsiveness to \( \beta \)-adrenergic stimulation (\( \beta \)AS) is characterized by a decrease in heart rate (HR) augmentation, left ventricular dilatation, and a decrease in contractility during exercise. When stress-induced plasma catecholamines (epinephrine and norepinephrine [NE]) were found to be higher in older compared with younger adults, investigators turned their attention to possible postsynaptic mechanisms to explain the blunted stress response. Further evidence supporting an age-related postreceptor alteration is the diminished contractility and HR augmentation of aged myocardium to exogenous catecholamines. The report by Orchard and Lakatta (see summary) of an age-related change in myoplasmic Ca\(^{2+}\) transients in response to NE, prompted Xiao and colleagues to test several stages of the postreceptor cascade leading to contractility in an attempt to identify (a) specific age-related change(s). The authors assessed the relative contributions of the inward Ca\(^{2+}\) current (sarcolemmal) \( I_{\text{Ca}^{2+}} \), the cytosolic Ca\(^{2+}\) transient, and the contractility of myocytes isolated from hearts of rats of three age-groups, 2, 6, and 24 months old. Calcium levels were measured using a fluorescent Ca\(^{2+}\) probe and \( I_{\text{Ca}^{2+}} \) was quantified by the voltage clamp technique.

Myocytes from rat hearts from the various age-groups were first observed for baseline contractile performance. No age-associated difference was noted in the twitch amplitude or maximum shortening velocity despite a slightly increased diastolic length in the oldest cells. The Ca\(^{2+}\) transient during baseline contraction was also consistent across age-groups, however, the ratio of Ca\(^{2+}\) in diastole was higher in older cells.

Excitation-contraction (E-C) coupling is initiated by an initial membrane depolarization, which triggers the \( I_{\text{Ca}^{2+}} \) through the sarcolemmal Ca\(^{2+}\) channels. The \( I_{\text{Ca}^{2+}} \) triggers a Ca\(^{2+}\)-dependent Ca\(^{2+}\) release from the sarcoplasmic reticulum (SR), where it is recycled after contraction through a Ca\(^{2+}\)-dependent ATPase pump. No age-associated compromise in the intrinsic E-C mechanism was justified by the normal resting performance. After exposure to increasing concentrations of NE, the younger myocytes demonstrated increased twitch amplitude and velocity with an increased \( I_{\text{Ca}^{2+}} \). In contrast, aged myocytes display a diminished contractile response (twitch amplitude and velocity) and decreased \( I_{\text{Ca}^{2+}} \) to increasing concentrations of NE. The amplitude and maximal rate of rise of the Ca\(^{2+}\) transient are surrogate measures for the excitation-induced release of calcium from the SR. In addition to a decreased SR Ca\(^{2+}\) release, relaxation, which is governed by Ca\(^{2+}\) sequestration by the SR, is also prolonged. The authors postulate that altered recycling of Ca\(^{2+}\) may be related to decreased phosphorylation of SR phospholamban by \( \beta \)AS.

To ensure that the results of these experiments were not influenced by the small amount of \( \alpha \)-adrenergic stimulation of the mixed agonist (NE), the studies were reperformed with the \( \alpha \)-adrenergic blocker prazosin, and yielded similar results.

This elegant series of experiments shed light on the role of intracellular Ca\(^{2+}\) cycling in the diminished contractile response of age myocardium to catecholamine stimulation. The investigators provide evidence that an initial decrease in \( I_{\text{Ca}^{2+}} \) contributes to the age-associated decrease in myoplasmic Ca\(^{2+}\) transient and thus contractility. Moreover, a delay in SR Ca\(^{2+}\) recycling may contribute to the delay in diastolic relaxation. These observations may help us to better understand the decreased response of the older heart to stress and, hence, where to target therapeutic interventions.

Martina Navratilova plays her final singles tennis match after a peerless career; Russian aircraft bomb the Chechen capital of Grozny; and Chandrika Kumaratunga’s Peoples’ Alliance party sweeps to power in the Sri Lankan general election.
Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women


J Appl Physiol. 1995;78:890-900

The effort to understand why older individuals have a decreased exercise capacity continues. To this point, it was accepted that with increasing age, heart rate (HR) augmentation and cardiac contractility are diminished. The new hot topics of debate in the 1990s were (i) were there specific gender differences in exercise? and (ii) did the Frank-Starling mechanism actually apply to humans?

Three unique spins to the exercise story underscore the significance of this work by Fleg et al for our understanding of the relationship between exercise and age. First, the application of a new technology, gated cardiac blood pool scans, provided insight into the changes in cardiac volumes at rest and during exercise. Previous correlation with cardiac catheterization validated this technique, which is now used for noninvasive assessment of cardiac performance during exercise. Second, the primary goal of the investigators was to understand gender differences in cardiac performance at rest and during exhaustive exercise. To this end, 79 female and 121 male healthy volunteers from the Baltimore Longitudinal Study of Aging (BLSA) were studied. Third, the subjects in this study were rigorously screened and excluded for any evidence of overt or occult cardiovascular disease. Exclusion criteria included any cardiovascular diagnoses or medications, an abnormal electrocardiogram, or a positive exercise stress test. Moreover, subjects over 40 had to confirm no evidence of coronary disease on an exercise thallium test.

Resting hemodynamics revealed a decrease in HR and an increase in systolic blood pressure (SBP) with increasing age in both genders. However, women had higher HR and lower SBP than men. A 46% increase in total peripheral vascular resistance (TPVR) and a 16% decrease in cardiac index (CI) was noted in women at rest, but not in men. On the other hand, resting cardiac volumes (end-diastolic and systolic volume index [EDVI and ESVI] and stroke volume index [SVI]) increased roughly 20% across the age span in men, but remained unchanged in females. Measures of cardiac pump function at rest, such as ejection fraction and myocardial contractility (SBP/ESVI), were not influenced by age in either gender, but were consistently higher in women.

As in prior studies, the exercise capacity of older men and women was diminished by 40%. At peak effort in both genders, an age-related decline in EF, HR, and CI, and an increase in SVI and TPVR compared with younger subjects were noted. The cardiovascular mechanisms used to attain peak performance, however, varied greatly according to gender. During exercise, the HR of women increased at a steeper rate than that of men. This may be compensatory for the smaller cardiac volumes seen in women. In contrast, men rely more heavily on the Frank-Starling mechanism to increase cardiac performance. Not only did men have higher cardiac volumes at rest, but during exertion, EDVI and ESVI remained higher than in women. To maintain the same SVI as younger subjects during exercise, older men, but not women, had a significantly elevated EDVI. As expected, ESVI increased during exercise in both genders, but was not influenced by age. Thus, the relationship between EDVI and SVI in older men during exertion is shifted upward and to the right compared with younger men and women.

In summary, cardiac reserve during exercise is blunted in both genders, but the specific hemodynamic strategies brought into play in women and men during exercise are unique. Men rely more heavily on the Frank-Starling mechanism to preserve SVI, whereas women depend on an increased heart rate. Consistent with the findings of Port et al (see summary) and despite rigorous screening, peak cardiac pump performance (EF, CI, and SBP/ESVI) declined with age, although SVI was not influenced by age.

British trader Nick Leeson is arrested for his role in the collapse of Barings Bank PLC; The graves of Czar Nicholas and his family are found in St Petersburg; and poison gas is released in the Tokyo subway, killing 12 and injuring thousands more: the attack is linked to the Aum Shinrikyo religious sect.
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<td>Bader H.</td>
<td>Dependence of wall stress in the human thoracic aorta on age and pressure.</td>
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