

III. CHARACTERISTICS OF SPECIFIC CARDIOVASCULAR DISORDERS IN THE ELDERLY

Human Aging: Changes in Structure and Function

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The rate of decline of function of the cardiovascular system with aging varies dramatically among individuals. This implies that multiple factors modulate a "biologic clock" or genetic mechanisms that determine the impact of age on the circulation. Thus neither differences among age groups in cross-sectional studies nor changes with time in a given individual in longitudinal studies are necessarily manifestations of "aging."

Factors That Modulate Aging

Occurrence of disease. One factor that modulates aging is the occurrence of disease. Disease and aging have to be specifically delineated to be able to identify and characterize the latter. This is not difficult when clinical signs and symptoms of a disease are obvious. However, occult disease may cause marked functional impairment. For example, asymptomatic ischemia may cause ventricular dysfunction (1). This is an especially pertinent consideration in studying the effects of age on cardiovascular function in humans, because the prevalence of coronary atherosclerosis increases markedly with age and is more often occult than overt in elderly persons. Although a high percentage of elderly individuals have coronary stenosis at autopsy, a much lower percentage have symptoms while living. It is imperative to detect the occult form of this disease to determine whether interventions, for example, a change in life-style variables, will have an impact on its progression; or to develop pharmacologic therapies to retard its progression. Because cardiac function, particularly during stress, is dependent on coronary blood flow, it is critical to detect occult coronary disease when investigating the impact of aging on myocardial function.

Changes in life-style. These also occur concomitantly with advancing age. They include changes in habits of physical activity, eating, drinking and smoking. Habitual exercise considerably changes both the function and the size of the heart, and this must be considered in interpreting the results of studies of the effect of aging on cardiac reserve. For example, there can be a 50 to 75% difference in cardiac output at peak exercise among individuals with different

activity states (2). Changes in cardiovascular function attributed to "aging" may be due in part to a sedentary life-style. The average daily physical activity level declines progressively with age in unselected populations (3) and undoubtedly decreases more in chronically institutionalized persons than in elderly people living independently in the community. This may seriously hamper the interpretation of studies examining the effects of aging on cardiovascular function in residents of a nursing home. Because the prevalence of occult coronary disease increases sharply with aging and major changes in life-style occur as well, their effects and the effects of an "aging process" on the cardiovascular system are interactive. This renders the identification of specific aging changes a formidable task.

Arterial Stiffness and Pressure

Unlike the vascular intimal changes that occur with atherosclerosis, the increase in vascular stiffness that accompanies advancing age apparently results from alterations in the vascular media.

Effect of aortic changes. With increasing age beyond maturity and into senescence the aorta undergoes progressive dilation and elongation, with increased stiffening of its wall (see [4] to [6] for reviews). The aortic wall becomes thicker and considerable reduction of aortic distensibility occurs. Between the ages of 30 and 80 years, the volume of the thoracic aorta can increase up to fourfold. These changes have been confirmed by postmortem examination as well as by in vivo assessment of aortic size by echocardiographic and radiographic examination. These alterations are due to a reduction of the amount of elastic tissue, to its fragmentation and degeneration as well as to an increased amount of collagen, and perhaps to structural changes in the collagen. As a direct result of the decrease in vascular distensibility, arterial pulse pressure increases; this is secondary to an increase in systolic pressure with less change in diastolic pressure (5). Because the aortic elastic tissue and smooth muscle do not sustain forward blood flow by decreasing the aortic size during diastole, a larger share of the burden of forward flow is imposed on the left ventricle

during systole (4). Both the reduced distensibility and the increased volume of blood that has to be accelerated during systole increase the impedance to blood flow (5,6).

Increased pulse wave velocity. Another manifestation of arterial stiffening is the increased pulse wave velocity with age. The conclusion that this increase in vascular stiffness is a manifestation of "normal" aging can be seriously challenged by cross-cultural studies showing that populations with differing life-styles also differ in the magnitude of increase in arterial stiffness with age (7). In China, the age-related vascular stiffening and arterial pressure are accelerated in the Beijing population, as compared with the rural southern (Guangzhou) population (7); the former, on average, excretes three times as much sodium. Although there is a statistically significant trend for arterial systolic pressure to increase with age in the United States, there is a wide scatter among individuals (1); this may be partly due to differences in life-style.

Cardiac Structure

Left ventricular hypertrophy. Progressive left ventricular hypertrophy with age occurs concurrently with the rise in arterial systolic blood pressure. Autopsy data from 7,112 human hearts showed that, among subjects between the ages of 30 and 90 years, the heart mass increased an average of 1 g/year in men and 1.5 g/year in women (8). The ratio of heart weight to body weight also increased. Between ages 30 and 80 years, the increase in heart weight corresponded to the age-dependent rise in the mean arterial blood pressure. Echocardiographic studies of 100 subjects without heart disease showed that both systolic and diastolic left ventricular wall thickness increased progressively with age in both sexes (9). Data collected from 105 male participants in the longitudinal study program of the National Institute on Aging revealed similar increases in left ventricular wall thickness with increasing age (10). Both the postmortem and the echocardiographic data are consistent, although the less specific electrocardiographic evidence of left ventricular hypertrophy does not clearly increase with age (4). The moderate myocardial hypertrophy with aging appears to be a successful adaptation that maintains normal heart volume and pump function in the presence of increased arterial pressure (11).

Myocardial collagen and amyloid. Although the increase in heart mass can be accounted for primarily by an increase in average myocyte size (12), a simultaneous change in the amount and physical properties of myocardial collagen may also play a role in causing the functional cardiovascular abnormalities of aging. Studies in humans have shown that the cardiac muscle to collagen ratio remains constant or increases slightly in the older heart. Further, human cardiac muscle loses its ability to swell with advancing age, suggesting that the myocardium becomes more rigid. More

recent studies have shown that this increased myocardial stiffness with age is due to an increased rigidity of the intercellular collagenous connective tissue. Changes in the cross-linking of collagen fibers probably account for these altered physical characteristics (4). There is an increase in the amount of lipofuscin, but this has no known functional significance.

Age-associated accumulation of amyloid in the human heart is also well recognized (13); it is not seen before age 65 years and its incidence correlates strikingly with increasing age thereafter. Whether cardiac amyloid can be considered a feature of normal aging is debatable because it is not an invariable finding, even in centenarians. "Senile" cardiac amyloid has two immunologically distinct forms, one limited to the atria and the other found in ventricular deposits and in minor extracardiac deposits that are often associated with ventricular involvement. Using sensitive and specific histologic staining methods, amyloid can be detected in the cardiovascular system in nearly half of patients >70 years of age, with the frequency increasing sharply thereafter. About half of the hearts have only minor quantities of amyloid, which is confined to the atria. Cardiomegaly is not a feature of senile cardiac amyloidosis, unlike that seen in the much rarer primary amyloid that may also occur in the elderly. In the senile form, amyloid accumulation is associated with myofiber atrophy and the firm, large, waxy heart does not occur.

Cardiac Function

Decreased ventricular compliance. Alterations in the physical properties of the heart and prolongation of the isovolumic relaxation period result in incomplete relaxation during the early diastolic filling (14,15), and apparently cause the decrease in early left ventricular diastolic compliance. This is manifest as a 50% reduction between the ages of 20 and 80 years in the rate of left ventricular filling during early diastole (10). Additionally, the changes in end-diastolic volume during postural maneuvers that alter venous return are decreased in older subjects. This also has been attributed to a decrease in ventricular compliance (16). Thus, cardiac hypertrophy and an age-related reduction in left ventricular compliance cause the aging heart to resemble the hypertensive heart (14).

Enhanced late diastolic ventricular filling. Although the rate of early diastolic left ventricular filling is reduced, left ventricular end-diastolic volume does not decrease with age (16,17). Enhanced ventricular filling later in diastole, due in part to an augmented atrial contribution to ventricular filling (18), is another adaptive mechanism to maintain an adequate ventricular filling volume in elderly subjects (16). The atrial contribution is manifest by the presence of a fourth heart sound. Older and younger individuals have the same stroke volume to end-diastolic volume relation, both at rest

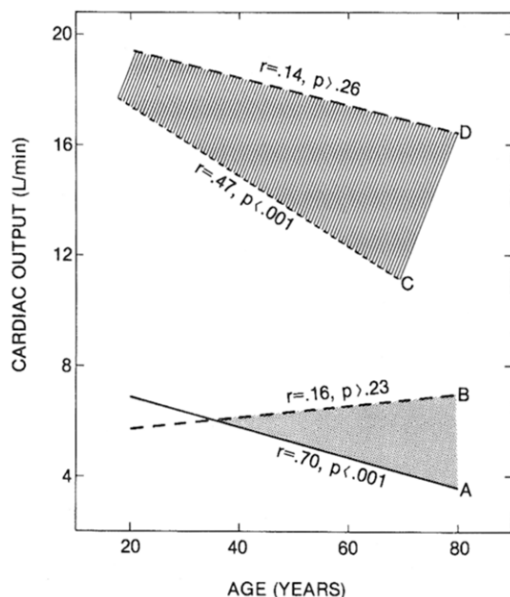


Figure 1. The best fit linear regression of cardiac output on age at rest (lines A and B) and during bicycle exercise (lines C and D). Regression lines B and D are derived from healthy, active, community-dwelling volunteers (17) screened to exclude coronary disease by exercise electrocardiography and thallium scintigraphy. In this group, cardiac output does not significantly decrease with age. In contrast, the subjects depicted by line A were hospitalized patients recuperating from noncardiac illness (20), and those depicted by line C were ambulatory volunteers who did not undergo prior exercise screening to exclude coronary disease (21). In these populations there was an age-related decrease in cardiac output. (Adapted with permission from Lakatta EG [20].)

and during exercise (16,17), but they function on different portions of this curve, particularly during exercise (see later). Although end-diastolic volume does not decrease with aging, because ventricular compliance is reduced, the end-diastolic pressure is often higher in older subjects, particularly during exercise.

Cardiac output. The cardiac output at rest decreases or remains unchanged with aging (19), depending on the population selected for study (Fig. 1). Stroke work at rest increases with age because of the increase in arterial pressure, even in populations in whom cardiac output decreases (1,21). The rest ejection fraction is not age-related in healthy subjects (10,17).

Cardiovascular Responses to Exercise

Age-related changes in the cardiovascular system might be anticipated to be most pronounced in response to exercise, when indexes of cardiovascular function such as cardiac output may increase up to four or five times above the basal level. During exercise, the level of cardiovascular performance is determined by complex interactions of basic

cellular and extracellular biophysical mechanisms. Most of these mechanisms are subject to autonomic modulation. Therefore alterations in cardiovascular function during exercise due to aging (or disease) can be attributed to the effect of age on basic (intrinsic) cellular mechanisms or to the autonomic modulation of these mechanisms (1).

Cardiac output and stroke volume. The apparent effect of age on cardiac output during exercise, as well as at rest, has varied among studies (Fig. 1) depending on the subjects selected for study (19). The increase in heart rate during vigorous exercise is less in elderly persons (4,19). However, in some subjects aged 65 to 80 years who were rigorously screened to exclude occult coronary disease and whose rest cardiac volume or output was not reduced, stroke volume during exercise increased more than in younger individuals and compensated for the lesser increase in heart rate (Fig. 1C and 2). As shown in Figure 2, subjects of all ages exhibit comparable increases in left ventricular end-diastolic volume during upright exercise at low work loads. At higher work loads, in younger individuals, as the heart rate accelerates, end-diastolic and end-systolic volumes decrease and stroke volume plateaus. However, in older individuals whose heart rate increase is less, increases in left ventricular volume and stroke volume continue throughout exercise, an example of the Frank-Starling mechanism. In other studies, elderly individuals had a lesser increase of both stroke volume and heart rate during exercise (22,23); the cardiac output at rest decreased with age, and left ventricular end-diastolic and end-systolic volumes were not measured. A study of another population aged 20 to 50 years, whose rest end-diastolic and end-systolic volumes decreased significantly with age, showed that an apparent age-related decrease in exercise cardiac output could be attributed exclusively to the decrease in heart rate because stroke volume during exercise was not age-related (24). However, the inclusion of joggers in this study may have had an impact on the ventricular size at rest and, thus, on the changes that occurred with exercise. Also, the age range was narrow and the possibility that different physiologic adaptations to exercise may occur in individuals >50 years was not examined.

Ejection fraction. Studies using radionuclide cineangiography have documented that left ventricular ejection fraction decreases or fails to increase progressively with increasing exercise in subjects with coronary artery disease. It has been suggested that similar reductions in left ventricular ejection fraction from rest to exercise could also be attributed to aging (Fig. 3A). However, occult coronary artery disease or cardiomyopathy was not systematically excluded in some studies and may explain the results obtained. Wall motion abnormalities, as determined by radionuclide cineangiography, may occur in as many as 30% of individuals >60 years (25). By contrast, in elderly subjects screened by noninvasive tests to exclude occult coronary

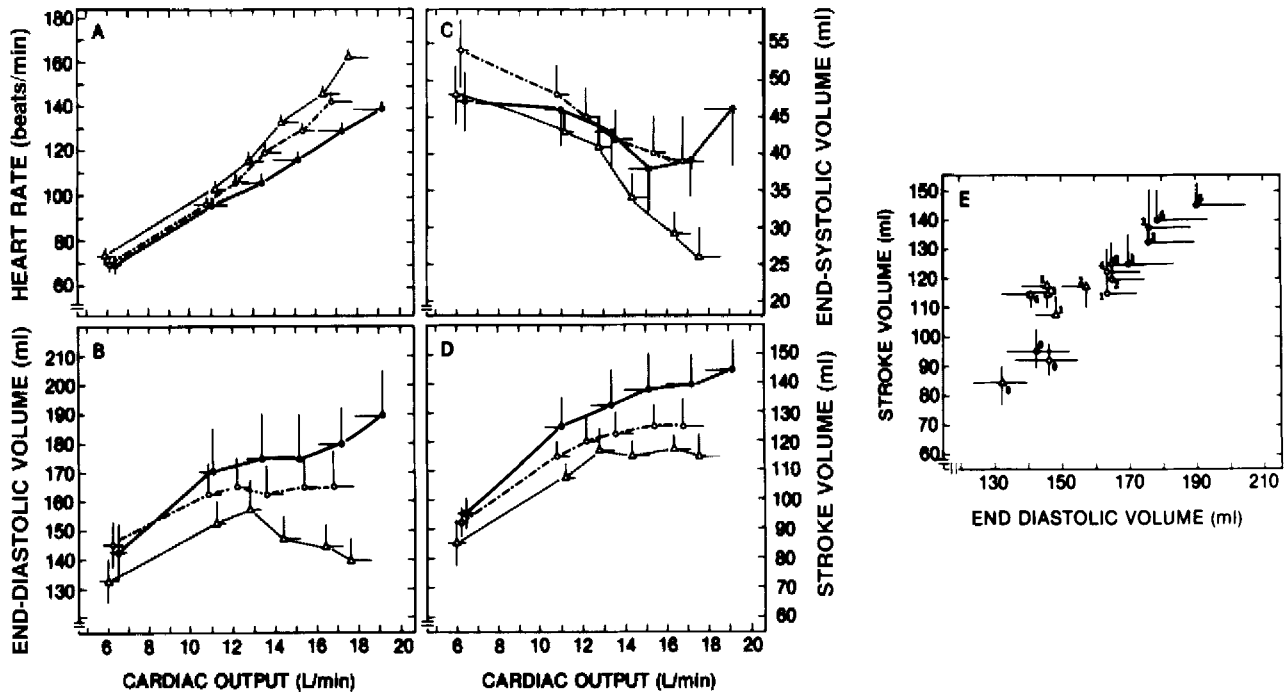
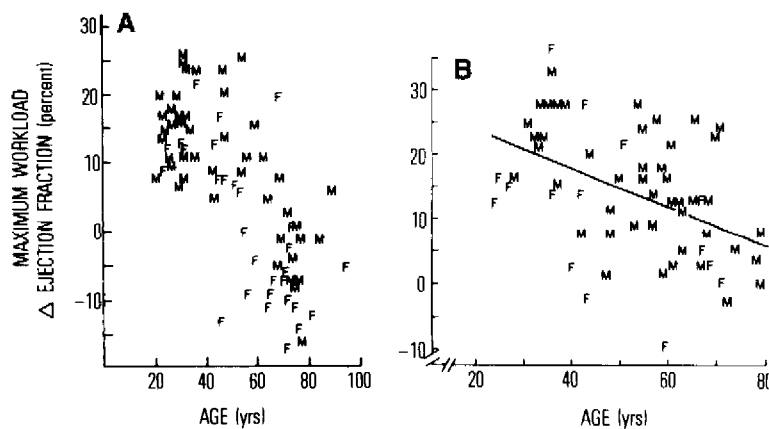


Figure 2. The relation of heart rate (A), end-diastolic volume (B), end-systolic volume (C) and stroke volume (D) to cardiac output at rest and during graded upright bicycle exercise in healthy subjects screened before study by the method described in Figure 3B. The major point of the figure is that a *unique* mechanism for augmentation of cardiac output during exercise does not exist in all subjects. To achieve the same high output as younger subjects, older subjects increase heart rate (A) to a lesser extent but increase stroke volume (D) to a greater extent than the younger subjects; that this is not accomplished by a greater reduction in end-systolic volume (B) compared with rest volume is depicted in E (0 = rest; 1 to 5 = progressive increments in work load). This hemodynamic profile is an example of Starling's law of the heart. Age in years: (Δ) 25 to 44; (\circ) 45 to 64; (\bullet) 65 to 80. (Redrawn with permission from Rodeheffer RJ, et al. [17].)

disease, although the ejection fraction at maximal exercise often did not increase to the same extent as in younger subjects, a reduction in ejection fraction below the basal level was rarely observed during exercise (Fig. 3B).



Autonomic Modulation of Cardiovascular Function

The hemodynamic profile of some elderly subjects during exercise is strikingly similar to that of younger subjects during exercise with beta-adrenergic blockade (26). Abundant evidence suggests that changes in the cardiovascular response to stress with aging in otherwise healthy individuals may be due, in part, to a reduction in the beta-adrenergic modulation of cardiovascular function (26,27). Data in humans and from animal tissues suggest that this altered response is partly due to a reduced effect of catecholamines on atrial pacemaker cells, vascular smooth muscle cells and cardiac myocytes (26,27). This may result from higher circulating levels of norepinephrine in elderly subjects during exercise and a reduced responsiveness at the receptor level.

Aerobic Capacity

Age and maximal oxygen consumption ($\dot{V}O_2$ max). There is continuing controversy as to which factors limit

Figure 3. A, Effect of age on change in left ventricular ejection fraction from rest to maximal voluntary exercise in apparently healthy subjects. (Redrawn with permission from Port S, et al. [25].) **B,** Effect of age on change in left ventricular ejection fraction from rest to maximal voluntary exercise in rigorously screened volunteer subjects from the Baltimore Longitudinal Study of Aging. (Redrawn with permission from Rodeheffer RJ, et al. [17].) F = female; M = male.

aerobic work capacity, assessed as maximal oxygen consumption ($\dot{V}O_2\text{max}$), in individuals of a *given* age. Further, it is not known whether the same factors are limiting in subjects of different ages (2,19). $\dot{V}O_2\text{max}$ is defined as a plateau in $\dot{V}O_2$ at two successive work loads. Most studies of the effect of aging on $\dot{V}O_2\text{max}$ have not demonstrated this plateau. Additionally, the extent of the decline in maximal work capacity with advancing adult age varies with life-style features such as physical conditioning and with the presence of occult or clinically evident disease (28). Elderly subjects are generally less well "physically conditioned" than their younger adult counterparts for a variety of reasons, including motivation and orthopedic impairments.

Factors in age-related reduction in $\dot{V}O_2\text{max}$. Muscle mass declines substantially (10 to 12%) with age, even in individuals whose total body mass is maintained (29,30). Thus, normalization of $\dot{V}O_2\text{max}$ for total body mass does not account precisely for differences in lean body (muscle) mass. A decline in peak $\dot{V}O_2$ with age cannot be considered due to an age-related decline in central circulatory performance unless an age difference in muscle mass or in the ability to shunt blood to exercising muscles can be excluded. This is important, because a greater than 10-fold increase in blood flow and oxygen utilization by muscle occurs during exercise. A recent study (29) showed that, although peak $\dot{V}O_2$ normalized for total body mass declined with age, normalization for 24 hour creatinine excretion as an index of lean body mass markedly reduced the apparent "age effect." These limitations invalidate the interpretation of the peak measured $\dot{V}O_2$ as the true $\dot{V}O_2\text{max}$. Because of these formidable obstacles to the interpretation of measurements of peak $\dot{V}O_2$ in elderly subjects, the extent to which $\dot{V}O_2\text{max}$ declines due to age itself and the mechanisms for this decline have to be reassessed.

The central circulatory function may not limit the peak $\dot{V}O_2$ achieved during exercise in the elderly, even though heart rate and stroke volume or cardiac output at exhaustion are lower in older subjects. Studies to date have failed to demonstrate a plateau in cardiac output and have been interpreted as indicating that the cardiac response at the $\dot{V}O_2$ achieved in elderly subjects during exercise is comparable with that in younger subjects (22,23). These studies provide no evidence that maximal cardiac function in elderly subjects was adequately tested, that is, that these subjects stopped exercising for cardiovascular reasons. Measurements of cardiac output during exercise fail to substantiate that cardiac output limits peak $\dot{V}O_2$ or work capacity in elderly subjects. This notion continues to be popular and is based on estimates of cardiac output from measurements of peak $\dot{V}O_2$ and heart rate and on extrapolated estimates of maximal stroke volume (28) and arteriovenous oxygen A-V O_2 difference (31) measured at lower work loads or in younger individuals. Such extrapolation requires the assumption that the relation between peak $\dot{V}O_2$ and cardiac output is common

to all individuals. It specifically ignores the changes during exercise in the peak A-V O_2 difference (22) and stroke volume (22) (Fig. 2) that occur in many older individuals.

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