

Review Article

Aging and the Cardiovascular System

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The progressive aging of the population is a phenomenon of our era. Aging is characterized by a progressive organ dysfunction that complicates the maintenance of homeostasis. However, there is no universal definition of senility. Physiological changes occurring with aging do not appear at any definite time. The majority of definitions of aging are based on calendar age. The World Health Organization defines senility as the age of >60 whereas according to most American classifications the borderline between maturity and senility is 65 years. Gerontologists distinguish between 3 subgroups: younger older people (60-74 years), older people (75-85 years) and very old people (>85 years).¹ Due to the fact that a considerable decrease in physical and mental efficiency occurs much more frequently beyond the age of 80, clinicians distinguish between 2 subgroups of older patients: those under and those above that age.¹

According to epidemiologic data, in USA the population of people who are aged above 65 years is expected to increase from 35 million in 2000 to 87 million in 2030, a percentage of 147%. At the same time, the population over the age of 85 years is expected to increase by a percentage of 389%. The incidence of cardiovascular diseases (CVD) increases linearly with age. Indeed, more than 70% of males and females over 75 years of age present some clinically evident CVD.¹ Moreover, CVD constitute the first cause of mortality (roughly amounting to 80%) in in-

dividuals over 65 years of age. A knowledge of the physiology of the effect of aging on the structure and function of the cardiovascular system is essential for a better understanding of the pathophysiology of CVD in elders.

Aging and myocardium

Structural changes

Remodelling of the left ventricle

With aging, a moderate increase in the thickness of the left ventricular (LV) wall is observed, even in absence of arterial hypertension or another cause of afterload increase.² In fact, it is a concentric hypertrophy, which is characterized by hyperplasia of myocardial cells due to the parallel addition of sarcomeres.³ When the hypertrophy concerns the interventricular septum, it leads to LV outflow obstruction and thus to a further increase in afterload. One possible explanation of this mild hypertrophy in old people is the increased systolic blood pressure, although the contribution of neurohormonal and/or other factors is considered equally possible. The combination of LV wall thickening and a reduction of its length render the ventricle more spherical. In addition, dextral shift of the ascending aorta also contributes to this reformation (Figure 1).⁴

Valvular changes

Aortic stenosis

The prevalence of valvular aortic steno-

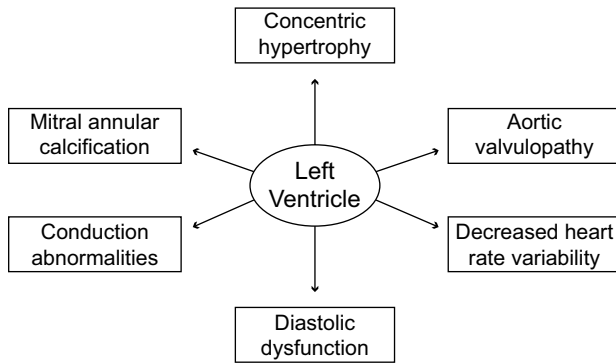


Figure 1. Diagram showing the changes in the left ventricle due to aging.

sis increases with age and is due to stiffening, scarring and calcification of the aortic valve leaflets. Aortic valve sclerosis is present in 80% of old people.⁵ Recently, degenerative aortic stenosis has been associated with decreased leukocyte telomere length, independently of possible confounding factors. This may be due to a telomere-dependent decrease in regenerative capacity associated with aging.⁶ Aortic sclerosis appears to evolve in step with atherosclerosis, explaining the increased risk of myocardial infarction and death in patients with aortic valve calcification. Indeed, older women and men who had aortic stenosis had a higher incidence of new coronary events than older persons who did not.⁷

Aortic regurgitation

The prevalence of aortic regurgitation increases with age, as a result of calcification of the aortic cusps and annulus. In a prospective study it was shown that 16% of older people had moderate to severe aortic regurgitation.⁵

Mitral annular calcification (MAC)

MAC is a chronic degenerative process that increases with age. In a prospective study the prevalence of MAC was higher in women (52%) than in men (36%).⁵ Subjects with MAC have a higher prevalence of atrial fibrillation, coronary events, heart failure, endocarditis, thromboembolic stroke and transient cerebral ischemic attack (Figure 1).⁸

Pacemakers - conducting system

The incidence of cardiac arrhythmias increases con-

siderably during aging, not only at rest but also during exercise. Indeed, with the increase of age a vital reduction of the sinoatrial node's pacemaker cells is observed, probably due to apoptosis, so that less than 10% of cells remain up to 70 years of age. In addition, the increased deposition of adipose tissue, amyloid and collagen, leads to sinus nodal disease.⁹ Comparable phenomena are also observed in the atrioventricular node and in the remaining electrical system of the heart. The abovementioned structural changes in the system of production and conduction of the stimulus influence the electric activity of the myocardium, leading to the clinical appearance of diseases.⁹ Indeed, a significant decrease in the sinoatrial node's pacemaker cells, combined with the increased deposition of adipose tissue, amyloid and collagen, leads to sinoatrial node disease. The foregoing structural changes exist to a smaller degree at the level of the atrioventricular node and bundle of His and to a greater degree within the bundle branches.⁹

Excitation - contraction coupling

In aging, the action potential and thus the duration of contraction are prolonged due to the prolongation of cytoplasmic Ca^{2+} release. The extension of the action potential is due to deceleration of the deactivation rhythm of L-type Ca^{2+} channels and the decreased outflow of K^+ .¹⁰ Also, the Ca^{2+} reuptake from the sarcoplasmic reticulum is decreased, while the activity of the Na^+-Ca^{2+} exchange pump is increased. Aging can also compromise the efficiency of Ca^{2+} spark signaling in cardiomyocytes, altering the pulsatile nature of Ca^{2+} in cardiomyocytes and impacting cardiac function.¹¹ The aforementioned changes in the Ca^{2+} cycle influence myocardial relaxation and are accountable for the deceleration of the premature diastolic filling rhythm, which characterizes aging.

Cellular - genetic changes

At the cellular level, a significant reduction of the myocardial cells is observed with aging. Indeed, from the age of 17 to the age of 90 years, 30-35% of myocardial cells are lost. The cell loss, which is smaller in females than in males, leads to hypertrophy of the adjacent cardiac cells, constituting a physiological compensatory process for the increased demands of the organism.¹² The mechanism of cell loss has not yet been fully clarified. It is probably the result of cell death (necrosis and/or apoptosis). Recent data indicate that

there may be a role for autophagy in cell loss. Furthermore, since telomeres mark the number of cell divisions, they are regarded as a biological counter and as such a marker of biological age. With aging, an important reduction in the length of telomeres and an absence of telomerase is observed, contributing to the aging of the organism, influencing cellular proliferation and thus survival itself.¹³ During aging the deposition of collagen is also increased. However, the ratio of collagen to myocardial cells remains stable because of the enlargement of the latter.

In addition, with aging, there are changes regarding the activation, contractility and relaxation of the myocardial cells, mainly due to modification of the expression of several genes. The aged myocardial cells are characterized by the following:

1. a decreased ability to respond to stress conditions (e.g. decreased heat shock protein expression);
2. decreased function of the mitochondrial respiratory chain (e.g. diminished expression of cytochrome c oxidase), with consequent oxidative damage;
3. reduced contractility due to decreased expression of the sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) and simultaneous transcriptional alteration of the contractive protein isoforms, from the fast into the slow myosin isoform (modification of genes that are related to the expression of SERCA and the Na/Ca exchanger likely explains the delayed relaxation of myocardial cells in aging);
4. the displacement of proliferation and survival signaling pathways to pathways of cellular death (e.g. decreased expression of the survivin protein);
5. the modification of genes that are related to the nucleus structure (e.g. decreased expression of the median fibrils Lamina A and C); and
6. the modification of genes that are related to cellular junctions (e.g. decreased expression of connexin 43, which is essential for cellular coupling and the gap junctions).¹⁴

Functional changes

Cardiac rhythm

Normally, the cardiac rhythm is regulated by the autonomic nervous system (ANS). Consequently, atropine causes tachycardia, while propranolol causes bradycardia. During aging, the abovementioned effects are decreased.¹⁵ Indeed, although vagotomy causes severe tachycardia in young lab-animals, it

does not in old ones. The malfunction of the ANS in aging is reflected by the decreased variability of cardiac rhythm.¹⁵ According to some studies, the decreased variability of cardiac rhythm constitutes a negative prognostic indicator.

Since cardiac rhythm is controlled by the ANS, it is affected by stressful situations, change of body position and breathing. At rest, the cardiac rhythm is not considerably altered with aging, whereas during exercise the maximum heart rate is lower in the elderly compared to young adults, reflecting the decreased reserves of cardiac output and the decreased aerobic ability of old people.¹⁶ The latter is due to an increase of body fat, decrease of muscle mass, and decreased stimulation of the sympathetic nervous system. In a supine position the cardiac rhythm of old adults does not differ from that of young adults. However, with the change of position from supine to upright, the cardiac rhythm of old people increases by a slightly smaller percentage than in the young.¹⁷ Normally, the cardiac rhythm is increased during breathing; a fact that decreases with aging, reflecting the decreased parasympathetic effect on myocardium.¹⁸

Systolic function

At rest the end-diastolic and end-systolic diameters of the LV are not changed with aging. Also, at rest the heart rate is not materially altered, or is slightly decreased in aged persons.¹⁹ Thus, systolic function and cardiac output remain normal.

Diastolic function

In contrast to systolic function, LV diastolic function is altered in old people. The aforementioned changes in the calcium cycle influence myocardial relaxation and are accountable for the deceleration of the premature diastolic filling rhythm that characterizes aging. Ultrasound and radionuclide studies have shown a 50% reduction of velocity of the early phase of LV filling between the third and ninth decades of life, with an equivalent increase in the late diastolic filling phase.²⁰ The delayed relaxation, combined with the decreased compliance of aged myocardium, leads to an increase in end-diastolic pressure, a decrease in the early passive diastolic filling phase, and an increase in the late energetic phase of diastolic filling. Consequently, the E/A ratio of mitral flow is decreased from 2:1 in an adult to 1:1 at the age of 60 years, reflecting the importance of atrial contraction

in LV filling and interpreting the low tolerance during atrial fibrillation that is often observed in these patients. Possible mechanisms that explain the reduction of velocity of the early diastolic filling are the extracellular matrix accumulation, fibrosis and the deceleration in calcium activation from the preceding contraction.²¹

The combination of decreased diastolic pressure and LV hypertrophy predisposes to subendocardial ischemia and development of fibrosis in the intermediate tissue. Ischemia further worsens the LV contraction (left and up shift of pressure-volume curve). The abovementioned changes decrease the compliance, and thus the filling of the LV, a fact that increases the pressure in the left atrium and pulmonary veins. Consequently, during aging a vicious circle begins that leads to development of diastolic heart failure, the most common form (40-80%) of heart failure in old people.²²

Aerobic exercise and aging

Aerobic capacity

With aging a progressive reduction in aerobic capacity is observed, as evaluated by maximum oxygen consumption (VO₂max). Even though the absolute VO₂max value is higher for males than for females, the rate of the decrease does not differ. According to recent data, VO₂max decreases by 30-40% per decade in healthy men and women. Notably, an average woman at the age of 80 years has a VO₂max of about 15-20 ml/kg/min, just as much as a middle-aged male patient with moderate degree heart failure. In aging the decrease of VO₂max is due to a parallel reduction of both cardiac output and arteriovenous oxygen difference. The maximum cardiac output is decreased mainly because of the reduction of maximum heart rate by 1 pulse/min/year. The reduction in the maximum arteriovenous oxygen difference (O₂) is accountable for 25% of the reduction of VO₂max and is involved in many mechanisms.²³

LV response to exercise

In aging, the stroke volume is mildly altered during intense aerobic exercise, while ejection fraction (EF) is considerably influenced, as is illustrated by the double increase in end-systolic volume compared to young adults. The maintenance of stroke volume is achieved via the Frank-Starling mechanism, accompanied by a

parallel increase in LV end-systolic volume. Therefore, during maximum exercise EF normally decreases from 85% in the third decade to 70% in the ninth.²⁴ Roughly 30% of men and 45% of women over the age of 60 years achieve an increase in EF of <5% during maximum exercise, an indication that is often used for the diagnosis of coronary heart disease.²⁴ Thus, old people are characterized by a higher restriction in their functional ability compared with younger patients who suffer from an equivalent disease. Consequently, during exercise, in order for the myocardium to satisfy the increased metabolic demands of the periphery it activates the Frank-Starling mechanism, thus increasing end-diastolic and end-systolic volume.

In addition, in aging, the response of the cardiovascular system to adrenergic stimulation is decreased.²⁵ During exercise, the function of an aged heart resembles that of a young adult who is under beta-blocker medication.²⁶ Furthermore, in aging, the inotropic response to digitalis is decreased, although the response to calcium is not, indicating that the signaling pathway is accountable for the insufficiency and not the contraction mechanism.²⁸

Aging and peripheral vessels

Structural changes of vessels

According to the BLSA study (Baltimore Longitudinal Study on Aging), during aging there are macroscopic and microscopic structural changes in the peripheral vessels that influence the blood supply of tissues and cardiac function.²⁸ Macroscopically the main changes observed are: 1) dilation and convolution of large arteries (dilation is more severe in the aorta proximal to the myocardium and in its large branches, but smaller in the muscular arteries); and 2) enlargement of the vascular lumen and thickening of the vascular wall.²⁹ However, the factors that are implicated in the progressive thickness of tunica intima and media in aging are not well known. Notably, the thickness of vascular wall constitutes an independent factor for future cardiovascular events (Figure 2).²⁹

Microscopically, endothelial cells become irregular in shape and increase in height. In addition, hypertrophy, proliferation and migration of smooth muscle fibers is observed in the subendothelial space, which is infiltrated by collagen deposits, while there is also a decrease and fragmentation of elastin as well as calcification. The amount of extracellular matrix is increased and becomes rich in glycosaminoglycans, thus decreas-

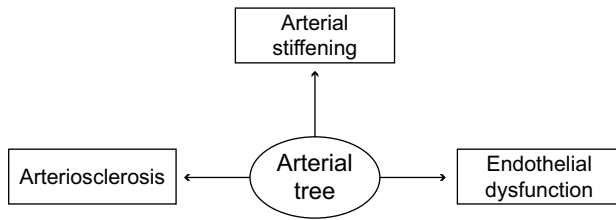


Figure 2. Diagram showing the changes in the arterial tree due to aging.

ing the vessels' compliance. Indeed, the compliance of the common carotid artery decreases by approximately 40-50% from the age of 25 to the age of 75 years. It is known that agents involved in the inflammatory/atherosclerotic processes, such as adherence molecules, matrix metalloproteinases, growth factors and cytokines, can occur in the tunica intima of arterial wall of old people.³⁰ At the cellular level, there is increasing expression of vasoconstrictive factors (such as endothelin-1 and angiotensin-II) and decreasing expression of vasodilator substances (such as estrogens and nitric oxide).³¹ Furthermore, an increased expression of angiotensin converting enzyme (ACE) has been documented in aortic wall, *in vivo* (Figure 2).

Functional changes of vessels

The abovementioned structural changes lead to arteriosclerosis, a condition that is distinct from what is described by the term atherosclerosis. Arteriosclerosis results in stiffening of the large arteries and an increase of pulse wave velocity (PWV), which is a reliable and widely used index of arterial stiffening.^{32,33} Changes in the shape of the arterial waveform also occur.³⁴ These changes are mainly characterized by an enhancement of the early systolic portion of the waveform as a result of the earlier return of the reflected wave from the periphery due to the increased pulse wave velocity. This early systolic enhancement increases left ventricular afterload and predisposes to disturbed myocardial oxygen demand/supply balance.^{32,33}

The increase in arterial stiffness with age is also responsible for changes in arterial pressure. Systolic blood pressure increases steadily, especially after the sixth decade, while diastolic pressure reaches a plateau after the fifth decade and decreases slightly after the sixth. These changes, taken together, result in a widening of pulse pressure from the sixth or seventh decade onwards.³² The resultant pulsatile stretch of

the large arteries endangers their wall integrity. Importantly, arterial stiffening (and especially its "gold-standard" index PWV) is an independent predictor of cardiovascular morbidity and mortality, as well as of total mortality, in a wide array of populations, including patients with hypertension or coronary artery disease, as well as the general population.^{32,33} Arterial aging is retarded by adopting a healthy lifestyle. Exercise in particular, even in the form of recreation, has a favorable effect on arterial stiffening with aging (Figure 2).^{32,33}

Concerning the pulmonary circulation, pulmonary artery pressure (PASP) increases with age (28% increase for each 10.6 years, $p=0.003$) in both men and women.³⁵ However, across age quartiles, the absolute increase in PASP is smaller compared with the increase in systolic blood pressure. The increase in PASP with age is related, at least in part, to age-associated vascular stiffening and pulmonary venous hypertension from left ventricular diastolic dysfunction.

Endothelial function

The increased sclerosis of vessels is the result, not only of the above vessel structural changes but also of the reduced endothelium-dependent vasodilation which is observed in humans with advancing age.³⁶ In senility, there is a decreased vasodilating response to acetylcholine, which concerns all vessels participating in the circulation, including coronary vessels.³⁶ The production and bioavailability of nitric oxide (NO) is decreased, resulting in vasoconstriction.³⁷ Furthermore, aging enhances the sensitivity of endothelial cells to apoptotic stimuli, impairs the angiogenic process and regenerative capacity of the endothelium, with a decrease in the number of circulating progenitor cells and their functional impairment with age.³⁸ In addition, the role of the endothelium as a barrier is altered and the permeability of endothelium is greater in young than in old persons (Figure 2).³⁷

The cellular and molecular mechanisms underlying age-associated NO decline have not been fully elucidated; however, they may include the gradual loss of antioxidant defense mechanisms, changes in expression or activity of endothelial NO-synthase (eNOS), and increased breakdown of NO because of enhanced O_2 production.³⁹ Furthermore, the reported age-dependent upregulation of the inducible form of NOS (iNOS) might contribute to increased ONOO- formation and thus to the oxidative damage of vascular tissue.³⁹

Therapeutic strategies

Myocardium

Data from meta-analyses do not support the claim that specific drug classes differ significantly in their ability to exert cardiovascular protection in younger and in elderly patients. The choice of the drugs to employ should thus not be guided by age. Thiazide diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, angiotensin receptor antagonists, and beta-blockers can also be considered for the initiation and maintenance of treatment in the elderly. Evidence is now available that antihypertensive treatment also benefits patients aged 80 years or more. Therapy should thus be continued or initiated when patients turn 80, starting with monotherapy and adding a second drug if needed.⁴⁰

A treatment-induced reduction in left ventricular mass is significantly and independently associated with a reduction of major cardiovascular events, stroke, and cardiovascular and all-cause mortality. Much less information is available on the comparative effects of different treatments on the diastolic abnormalities frequently occurring in elderly patients, often but not always concomitant with ventricular hypertrophy.⁴⁰

Vessels

Pharmacological treatments that are able to reduce arterial stiffness include: 1) antihypertensive treatment, such as diuretics, beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin receptor antagonists and calcium-channel antagonists; 2) treatments for congestive heart failure, such as angiotensin-converting-enzyme inhibitors, nitrates and aldosterone antagonists; 3) hypolipidemic agents, such as statins; 4) antidiabetic agents, such as thiazolidinediones; 5) sildenafil; and 6) AGE-breakers, such as alagebrium (ALT-711).⁴¹

Conclusions

Aging is characterized by structural and functional changes in the cardiovascular system, overt and occult cardiovascular disease, and reduced physical activity. In particular, aging is characterized by:

1. a loss of myocytes, with progressive increase in myocyte cell volume per nucleus;
2. hypertrophy of the remaining myocytes;

3. a progressive reduction in the number of pacemaker cells in the sinus node;
4. wall thickening;
5. diastolic dysfunction, which predisposes to the development of diastolic heart failure;
6. an increase in the systolic arterial pressure and pulse pressure, because of the increased pulse wave velocity and the ejection time delay;
7. endothelial dysfunction, which is a predisposing factor for atherosclerotic disease;
8. arterial sclerosis and increased systemic vascular resistance;
9. a delayed arterial baroreceptor reflex response, which influences the activity of the sympathetic nervous system and is accountable for the appearance of orthostatic hypotension;
10. a decreased cardiopulmonary reflex, which leads to electrolytic disturbances, derangement of body fluid homeostasis, and disturbance of the microcirculation;
11. decreased maximal heart rate, maximal cardiac output and maximal VO_2 .

However, it is difficult to distinguish the changes that are clearly related with age from the changes that have another etiology.

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