

# Senescence of the cardiovascular system due to aging and the resulting increase in cardiovascular risk.

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## Abstract

**Introduction:** The progressive senescence of earth's population constitutes one of the main determinants of demographic phenomena in modern times. Taking into account the correlation between age and cardiovascular diseases (CVD), it is a fact that the constantly raising number of elderly people with such problems will be of great interest to public health, in future.

The aim was to be comprehended how importance is to bear in mind by the clinician, the special problems of the older age during therapeutic interventions in these age groups.

**Method and material:** The method of this study included bibliography research from both the review and the research literature about aging and CVD .

**Results:** The increasing incidence of the CVD and the growing cardiovascular risk in the elderly basically relies on the "normal" senescence of the cardiovascular system ,the degeneration of the remaining systems of the organism ,the aggregation and the cumulative influence of the standard cardiovascular risk factors and at last at the presence of severe diseases caused by the other systems or geriatric syndromes. Degeneration of the cardiovascular system and remaining systems of the organism like lungs, kidneys, e.t.c., and diseases affecting other systems are the most common factors to CVD. The gradual, however, normal degeneration of the cardiovascular system in combination with the senescence of the other systems of the organism, which lead to parallel diseases, cause cardiovascular events, worsening the prognosis even further.

**Conclusion:** The clinician should be aware of all the procedures, which reduce the homeostatic supplies of the elderly, making vulnerable to life threatening diseases. The understanding of the psychological and the social status of the elder patient with cardiovascular problems and the synthesis of all the available data may lead to a global approach and to a proper treatment.

**Keywords:** Aging , cardiovascular system, cardiovascular risk

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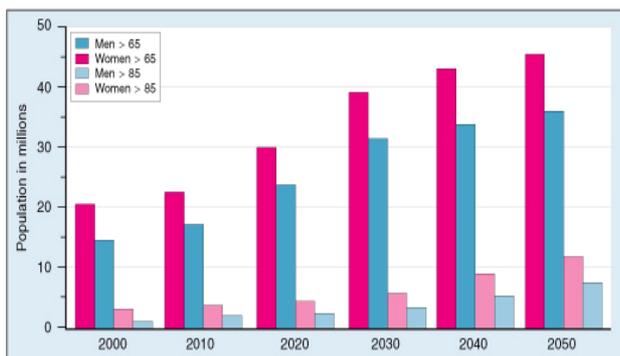
## Introduction

**T**he progressive senescence of earth's population constitutes one of the main determinants of demographic

phenomena in modern times. The recent demographic data from the western world come to the conclusion that the number of people over 65 years old is expected to raise

from 35.1 million in 2000 to 86.7 million in 2050, a percentage reaching 147%. The increase in the elderly group (aged over 85 years old) is expected to be much higher (approximately 389%) for the same period of time (Picture 1).<sup>1</sup>

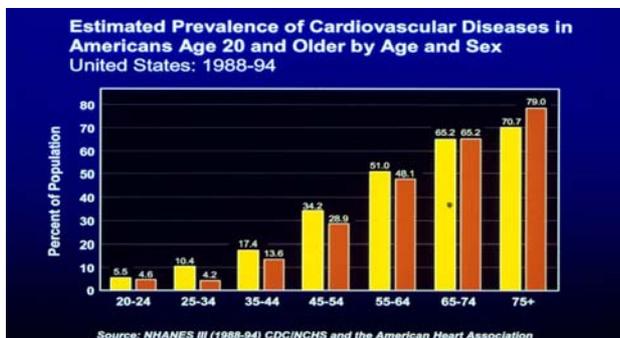
Picture 1. Population estimates in USA between 2000-2050



(The U.S. Census Bureau)

Taking into account the correlation between age and cardiovascular diseases (CVD), it is a fact that the constantly raising number of elderly people with such problems will be of great interest to public health, in future, as far as the primary and the tertiary health care is concerned. It is estimated the CVD rate of manifestation (including hypertension) exceeds 65% in the group of people older than 65 years old and it is indeed the primary cause of death and major disability (Picture 2).<sup>2</sup>

Picture 2. Prevalence of the cardiovascular disease according to age and sex



Yellow: men, Orange: women, (Ann Epidemiol 1997)

As far as coronary disease is concerned, its prevalence increases with age in men as well as in women, tending to reach the same level after the age of 70 years old in both sexes. In United States of America, a percentage higher than 60% of those who suffer an acute myocardic infarction are over 65 years old, whereas a percentage higher than 80% of deaths due to myocardic infarctions is met in the same age group<sup>3</sup>. Beyond the evident impact on the mortality rate, ageing substantially increases the number of readmissions with CVD. It is estimated that approximately 65% of the readmissions occurs in the age group of over 65 years old. Moreover, the need for medical interventions, that is, diagnostic catheterization, angioplasty, pacemaker and defibrillator implantations, cardiovascular surgeries, endarterectomy is multiplied, a situation that seriously aggravates patients' prognosis and the economic health system.<sup>2</sup>

The increasing incidence of the CVD and the growing cardiovascular risk in the elderly basically relies on four factors:

- the "normal" senescence of the cardiovascular system
- the degeneration of the remaining systems of the organism
- the aggregation and the cumulative influence of the standard cardiovascular risk factors
- the presence of severe diseases caused by the other systems or geriatric syndromes.

All the aforementioned mechanisms lead to a substantial differentiation as far as the clinical manifestations, the response to the treatment therapy and the prognosis of the CVD in the elderly are concerned. It is necessary to be fully aware of the pathophysiological stages of senescence in the structure and function of the cardiovascular as well as of other systems, in order to comprehend the clinical manifestations of these diseases in such populations.

A. Degeneration of the cardiovascular system is characterized by multiple disorders not only in its structure but also in its

function. The endothelial malfunction, the stimulation of the apoptosis process, the oxidative stress, the inflammatory process and the neurohormonal systems affect not only the heart system but also the peripheral vascular system.

#### Echocardiographic variations

**Remodeling of the left ventricle:** As people grow older a moderate and gradual increase in the arterial wall thickness of the left ventricle (LV) is noted, which rarely surpasses the upper normal values. A possible reason for this mild hypertrophy is the increase in the systolic blood pressure in the elderly, even though the contribution of several neurohormonal and other factors is possible. Despite the increase in the arterial wall thickness, the size of the left ventricle remains stable due to a decrease in its length (as it is observed in studies with magnetic resonance), remodeling the left ventricle in a spherical shape in the course of time.<sup>5</sup>

**Systolic function:** The end-diastolic as well as the end-systolic diameter of the left ventricle do not alter with ageing. Consequently, the traditional echocardiographic systolic markers (such as ejection fraction, fractional shortening) remain normal.<sup>6</sup> Since the pulse tissue Doppler has been applied in clinical cardiology, there have been controversial results as far as the systolic function of the LV is concerned, because its maximum systolic velocity ( $S_m$ ) is reduced, but, on the other hand, according to others the maximum systolic velocity ( $S_m$ ) does not change significantly with ageing. As far as the right ventricle is concerned, we should emphasize that there is no substantial variation in the tissue systolic velocity during senescence.<sup>7,8</sup>

**Diastolic function:** There is a gradual decrease of the elasticity of the myocardial tissue, a decrease in compliance and an increase in the ventricular stiffness, concluding in diastolic dysfunction. For this reason, in contrast to the systolic, the diastolic function of the left ventricle is characterized by significant variations with

ageing. It is demonstrated not only by echocardiographic but also by radioisotopic studies, a 50% decrease in the early diastolic filling of the left ventricle between the third and the ninth decade of life (a decrease of the wave E of the transmitral flow) and a relevant increase in the late diastolic filling (an increase in the wave A of the transmitral flow). So the ratio E/A of the transmitral flow from approximately 2:1 in the young adults decreases in 1:1 in the age of 60, to be reversed in the elderly ( $E < A$ , delayed relaxation), a fact which reflects the great significance of the atrial contraction in the filling of the LV in this age group and explains the bad prognosis in the development of atrial fibrillation, which occurs in this particular age group (e.g. the presence of symptoms of heart failure despite the satisfactory systolic function).<sup>9</sup> The pulse tissue Doppler supports the aforementioned disorders in the diastolic function, as a gradual decrease in the early tissue diastolic velocity  $E_m$ , an increase in the late  $A_m$  and finally a decrease in the ratio  $E_m/A_m$  (or a reverse of the ratio,  $E_m/A_m < 1$ ),<sup>7,8</sup> are detected. In fact, the same applies for the diastolic function of the right ventricle.<sup>10</sup> In conclusion, we may claim that in the absence of diastolic dysfunction, the structural and functional disorders, as regards the heart during ageing, are similar to those of mild hypertension: 1) an increased thickness of the left ventricle wall, 2) dilatation of the left atrium, 3) maintenance of a satisfactory systolic function and 4) a decrease in the early diastolic filling and respectively an increase in the late diastolic filling of the left ventricle.

#### Echocardiographic/ electrophysiologic variations

**Conduction system:** Multiple structural changes are observed in the conduction system, which may affect the electrical properties and lead to the clinical manifestation of the disease. These also include an increase in the elastic and collagenous fibers, as well as, in the adipose tissue in the interstitium. Up to the age of 60 a substantial decrease in the pacemaker cells

of the sinus is observed, so as in the age of seventy, less than 10% of the pacemaker cells remain alive in contrast to the young adult. This fact, in addition to the increase of the adipose tissue often leads to sinus disease. Also, the gradual calcinosis of the cardiac skeleton, which includes the aortic and mitral ring and the central fibrous body can expand to the atrioventricular node, to the His bundle, as well as its branches. This may also lead to atrioventricular conduction disorders. In fact, the coexistence of hypertension, coronary disease or cardiac senile amyloidosis may lead to clinical evident disorders. These anatomic disorders result in various disorders of the normal ECG of the healthy elderly people. It is worth mentioning that a substantial decrease in the heart rate variability is observed with ageing, which possibly is attributed to a disorder of the balance of the autonomic neural system and is linked to an increased rate of the cardiovascular events and total mortality.<sup>11</sup>

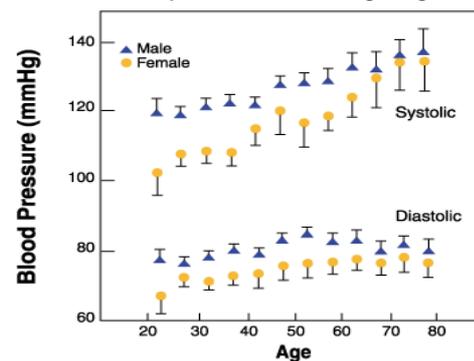
**Arrhythmias:** The prevalence and the complexity of the cardiac arrhythmias substantially grows with age, not only at rest but also during activity and 24 hour monitoring. These refer either to insignificant arrhythmologic findings (extraventricular and hyperventricular contractions) or to the manifestation of sick sinus syndrome (SSS), various grades of atrioventricular AV block and atrial fibrillation. The presence of atrial fibrillation correlated with an increased risk of thrombosis, which is detected in the elderly, is the reason for the quadruplication of the hazard of an imminent stroke.<sup>12</sup>

#### Peripheral vases

**Structural alterations:** The structural alterations which are observed with ageing in the vases and especially in the arteries may influence not only the peripheral hemostasis of the tissue but also the cardiac function. These are related to a decrease in the elastic fibers, as well as to an increase in the calcium rate and in the collagenous fibers of the arterial wall. The growth of the thickness of the arterial wall not only in the main

arteries but also in the peripheral arteries is demonstrated by the growth of the intimal-medial thickness (IMT), during triplex examination.<sup>13</sup> These structural alterations lead to an increased arterial stiffness, which clinically results to an increase of the systolic arterial pressure and the pulse pressure with ageing (Picture 3).

Picture 3: Variations in the systolic and diastolic blood pressure with ageing



(J Gerontol Med Sci 1997)

These parameters constitute strong risk factors for cardiovascular events. Moreover, the main arterial pressure is characterized by a postsystolic motion in the elderly due to an early emergence of the reflected wave from the periphery. The last two parameters, which are correlated with the arterial stiffness lead to an increase of the afterload of the LV, resulting in the growth of the wall tension and the oxygen consumption in the elderly. The speed conduction of the pulse wave is commonly used as an index of arterial stiffness, which grows in a parallel way with age.<sup>14</sup>

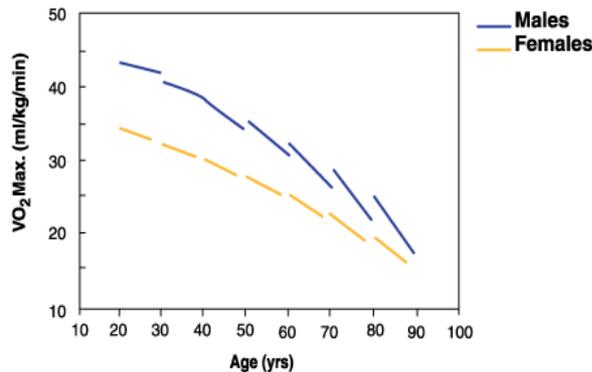
**Vasodilatory ability:** There is a progressive endothelial dysfunction which is attributed to ageing. So, in healthy adults we observe a decrease of approximately 75% in the endothelial-dependent vasodilation of the brachial artery within the age 40 to 70. The decrease is 2.5 times more abrupt in women, but it occurs a decade later due to the beneficial effect of the estrogens in the endothelial function.<sup>15</sup>

#### Response to the aerobic exercise

**Aerobic ability:** The aerobic ability for exercise as it is estimated by the maximum

oxygen consumption ( $VO_2\max$ ), is significantly reduced with ageing (Picture 4).

Picture 4: Relation between age and  $VO_{2\max}$  in healthy adults



(Circulation 2000)

According to recent studies,  $VO_2\max$  is reduced 30-40% per decade in healthy men and women aged 70-80 years old. It is worth mentioning that a normal woman of 80 years old has  $VO_2\max$  approximately 15-20ml/kg/min, that is the same values of a middle-aged patient with mild or moderate heart failure.<sup>16</sup>

**Components of  $VO_2\max$ :**  $VO_2\max$  is the product of the cardiac output and the oxygen arteriovenous difference during maximum exercise. The reduction of  $VO_2\max$  is the result of the parallel decrease of the two parameters with ageing. The maximum cardiac output is negatively affected mainly because of the decrease of the maximum heart rate of 1 pulse per minute per year. The reduction of the maximum oxygen arteriovenous difference is responsible for approximately 25% decrease of  $VO_2\max$  and is attributed to various possible mechanisms.<sup>17</sup>

**Left ventricular output during exercise:** Despite the fact that the stroke volume during intense aerobic exercise is hardly affected during ageing, the left ventricle ejection is substantially affected, as it is noted from the duplication of the end-systolic volume index, in contrast to young adults. The retention of stroke volume occurs with the parallel increase of the end-diastolic volume of the left ventricle (due to the Frank-Starling mechanism). So, the

ejection fraction during intense exercise in normal people (without coronary disease) is decreased from approximately 85% during the 3<sup>rd</sup> decade to 70% during the 9<sup>th</sup> decade. Approximately 30% of men and 45% of women aged older than 60 years old reach a less than 5% increase of the ejection fraction during intense exercise. This is commonly suggested as a criterion for diagnosing coronary disease. The aforementioned cardiovascular disorders during intense exercise are depicted in Table 1.

Table 1: Cardiovascular variations during intense exercise in the ages between 20 and 80 years old

Oxygen Consumption	reduction ~ 50%
AV oxygen difference	reduction ~ 25%
Cardiac output	reduction ~ 25%
Heart rate	reduction ~ 25%
Stroke volume LV	reduction ~ 15% - 25%
End-diastolic volume LV	No change or minor reduction
End-systolic volume LV	Increase ~ 150%
Ejection fraction LV	reduction ~ 15%

As a result of the above, an elder patient will most certainly develop major limitations of the functional ability in contrast to a younger patient with the same disease severity.<sup>18</sup>

**Response/sensitivity to b-adrenergic stimulation:** The hemodynamic profile during intense physical exercise in the elderly is similar to the application of the b-receptors block in younger people and is compatible with a reduced sensitivity of the b-receptors in the elderly. The reduced sensitivity of the cardiovascular system to the catecholamines limits the compensation mechanisms of the elderly, especially when he/she faces an urgent condition, such as a systemic infection, anemia, volume loss or any systematic attack, even in the absence of heart disease. The decrease in cardiovascular supplies most certainly

contributes to the worst prognosis of the elderly with cardiovascular disease. The decrease in the cardiovascular reserve and the inability to respond to the neurohormonal stress and the pre-inflammatory - cytokinetic activation leads to an increased sensitivity of ischemic events in the elderly and to the volume or pressure load. As a result, there is an increased prevalence of heart failure, of ischemic or other etiology. The reduction of the aerobic exercise of the elderly, the lack of response to exercise, the adrenergic stress and finally the deterioration of the physical status lead to short supplies of the elderly. This condition is mostly responsible for the poor prognosis of the elder patients.<sup>19</sup>

B. Degeneration of the remaining systems of the organism (lungs, kidneys, liver, central nervous system, hematopoietic and myoskeletal system), whose function is closely linked to the cardiovascular system. This correlation is evident with ageing. A closer analysis shows that the lungs lose their elasticity, which leads to a decrease in the vital capacity, the minute ventilation volume and to significant changes in the perfusion - ventilation rate, especially during intense exercise. The kidneys show signs of nephrosclerosis, nephron loss and decreased glomerular filtration rate, which results in a gradual decrease of the creatinine clearance (at a level of 50% between the 3<sup>rd</sup> and 9<sup>th</sup> decade). Moreover, the activity of the renin-angiotensin-aldosterone system is reduced, which consequently affects the homeostasis of the neurohormonal profile. The myoskeletal system gradually loses not only the osteal tissue but also muscular mass, that is why there is a substantial decrease in the functional ability and the quality of life of the elderly. This also constitutes a peripheral cause for the elderly to develop heart failure. The gradual decrease in the blood volume disrupts the oxygen transfer ability to the peripheral tissues, leading to further aggravation of the functional ability of the elderly. The emerging liver disease is able to affect to a great extent the homeostasis of the biochemistry of the

organism. The degeneration of the central nervous system is the cause of the weakening of the neural reflexes and its ability to self-regulation. In addition, it disrupts the thirst mechanism, consequently the fluid balance of the organism. Finally, a great number of major neuropsychiatric syndromes emerge, which are particularly harmful for the elderly patients.<sup>20</sup>

C. The traditional cardiovascular risk factors, that is smoking, diabetes mellitus, dyslipidemia and hypertension, which may lead to atherosclerosis and major cardiovascular events. These factors have an excellent prognostic value in the elderly people. In fact, their accumulation and their harmful effect in the cardiovascular system for a prolonged period of time increase the potential risk. Systolic hypertension is a strong risk factor for fatal and non fatal cardiovascular events (including strokes) in people over 65 years old. In contrast, the significance of diastolic hypertension as a risk factor fades with ageing. Recent data support the idea that increased pulse pressure is the most important cardiovascular risk factor for the elderly. A large number of prospective randomized trials have affirmed that the proper control of hypertension with diet or pharmaceutical interventions leads to the decrease in mortality and major cardiovascular events in people up to 90 years old.<sup>21</sup>

The importance of dyslipidemia as a risk factor for cardiovascular disease in the over-aged is ambiguous. In men, total and LDL cholesterol increases until the age of 65 years old and later on these gradually decrease. In contrast, women's values of total and LDL cholesterol increase rapidly after menopause and remain in a higher level than those of men, after the age of 65. HDL cholesterol has no such fluctuations and remains in a higher level of approximately 10 mg/dl, during women's life (Table 2).

Even though many studies (including Framingham heart study) supported the idea that the correlation between cholesterol levels and cardiovascular risk factor decreases with age, the most recent data

agree with the fact that the prognostic value of dyslipidemia still remains until the age of 80 years old. This conclusion is also confirmed by the observed benefit of the administration of hypolipidemic therapy (statins) in over-aged people.<sup>22</sup> In contrast to other risk factors, the prevalence of smoking is reduced with ageing either because of its cessation or due to smokers' early death. Nevertheless, 63% of deaths which are attributed to smoking occur in people older than 65 years old. In this way, the strong and continuous correlation between smoking and cardiovascular risk is confirmed regardless the age. Smoking cessation is of major importance not only as primary but also as secondary prevention of the over-aged people.<sup>23</sup> The prevalence of diabetes mellitus (DM) increases with age, reaching the level of 20% after the age of 65 years old. Diabetes mellitus is still considered a strong and independent risk factor even for older people, both in men and women.<sup>24</sup> Lately, diabetes mellitus is characterized as an equivalent of coronary disease and so it is strongly recommended we try an invasive glycemic regulation, close attendance and therapeutic approach of its complications.

Table 2: Cholesterol values according to age

Age	Total, mg/dl		LDL, mg/dl		HDL, mg/dl	
	Men	Women	Men	Women	Men	Women
20-34	189	185	120	110	47	56
35-44	207	195	134	117	46	54
45-54	218	217	138	132	47	57
55-64	221	237	142	145	46	56
65-74	218	234	141	147	45	56
≥ 75	205	230	132	147	45	57

Source: National Health and Nutrition Examination Survey (NHANES)

**D. Diseases affecting other systems** (such as, stroke, chronic respiratory failure, renal failure, anemia) further decreases the response mechanism of the organism towards these diseases leading to acute or chronic heart failure. The presence of geriatric

syndromes which are rather common in older people, is the reason that modifies their clinical condition, their response to therapy and the prognosis of cardiovascular events. The neuropsychiatric diseases (depression, dementia, mental disorders), the sensory organs disorders (hearing, sight), the incontinence, the homeostasis disorders (fluids-electrolytes, temperature, metabolism), the balance disorders (imbalance), the chronic reclination and especially the elderly's denial towards life, seriously aggravate their functional ability.<sup>25</sup>

The fact that major clinical studies in cardiology have excluded over-aged patients and especially those with multiple coexisting diseases makes scientists rather skeptical whether we should apply these results to this particular age group. Moreover, we should emphasize on the coexisting kinetic/dynamic particularities of all pharmaceutical substances, which are administered to the elderly and even more in over-aged patients. These particularities should always be taken into account during therapeutic interventions in these age groups.

So, the over-aged patient with cardiovascular disease should be treated with great caution due to the particularities of his age. His multilateral problems require the harmonious collaboration between doctors of varied specialties (such as cardiologists, pathologists, general practitioners, psychiatrists, physicians and other health professionals (such as nurses, sociologists, pharmacists), within the framework of organized units.<sup>20</sup>

#### Conclusion.

The clinician should be aware of all the aforementioned procedures which reduce the homeostatic supplies of the elderly, making vulnerable to life threatening diseases. The gradual, however, normal degeneration of the cardiovascular system in combination with the senescence of the other systems of the organism, which lead to parallel diseases, cause cardiovascular events, worsening the prognosis even further. It is, therefore, necessary to comprehend the

pathophysiology, the particularities of the cardiovascular system in the third age, but also to have an overall knowledge of all the other systems. Moreover, the understanding of the psychological and the social status of the elder patient with cardiovascular problems and the synthesis of all the available data may lead to a global approach and to a proper treatment.

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