President's Page

"Beware Old Age, for It Never Comes Alone"

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Τίμα το γήρας, ου γαρ έρχεται μόνον – Menander, 4th century BC

During the long course of human history, it is only during the last few decades that concerted efforts by the worldwide medical community have managed to break the "time barrier" and double our life expectancy. Thus, nowadays we are able to enjoy, with relatively ease, ages of 80 and 90 years. Epidemiological projections show that by 2030 the number of people aged over 65 years will be close to a billion, or 12%, while by 2050 this proportion will increase to 20% of the total population of the Earth.

Although we have managed to reach such advanced ages, our knowledge of the aetiological mechanisms of ageing still remains unclear. There is no generally accepted definition of "old age", nor any precise marker to show where it begins. As the physiological changes associated with ageing do not appear at any specific time and do not develop at the same rate in all people, most definitions of ageing are based on chronological age. The World Health Organisation proposes the age of 60 years to define "elderly", whereas most classifications in the USA propose the age of 65 years. The cardiological community often uses the subcategories of below 65, 65-74, 75-84, and 85 years or older, aiming to emphasise the significant differences that exist between these categories in relation to the performance of the cardiovascular system.

The molecular hypotheses regarding the age-dependent changes that occur in our body include oxidative damage, inflammatory responses to cellular stress, and programmed cell death. The cardiovascular system is perhaps the first system to be harmed by these mechanisms and to undergo ageing. Subsequently, the progressive deterioration of arteriosclerosis and atherosclerosis, in combination with a reduction in cardiac performance, interrupts the energy supplied to peripheral tissues, setting them on the road to dysfunction and death.[1]

In the arterial wall, cellular, enzymatic, and molecular processes lead to the migration of activated vascular smooth muscle cells to the intima, accompanied by an increased production of matrix, and increased collagen production due to impairment of the activity of metalloproteinases, angiotensin II, and intracellular adhesion molecules. A loss of elastic fibres is also observed, together with an increase in collagen fibres and calcium deposition. All this leads to an increase in intima thickness, arterial dilation, and arterial stiffness, resulting in increased pulse wave velocity, reflected waves, and pulse pressure. In both animals and humans, endothelial nitric oxide (NO) production decreases with advancing age. A reduction in the mass of endothelial cells is observed, because of increased cellular ageing and apoptosis, together with increased NO consumption due to the age-dependent increase in the production of vascular superoxide anion. At the same time, because of the intimal thickening, it becomes more difficult for NO to permeate the smooth muscle cells of the media, resulting in reduced vasodilation.[2]

Along with all the above vascular changes, similar changes also occur in the extracellular matrix of the myocardium. There is an increase in collagen and in the ratio of collagen type I to type III, a decrease in elastin content, and an increase in fibronectin. The balance between the metalloproteinases of the matrix and their tissue inhibitors is disturbed, favouring an increase in the production of extracellular matrix. These changes are accompanied by the

destruction of myocytes and an impairment of cellular function.

At the level of the atria there is a decrease in the number of sinus nodal cells and L-type calcium channels; these changes, in combination with those in the extracellular matrix, contribute to sinus node dysfunction and the appearance of atrial fibrillation. The changes in collagen and elastic tissue, together with calcification within or near to the central fibrous body and the atrioventricular node, or proximal to the bundles, contribute to conduction disturbances and to the calcification of valvular annuli. In the ventricles, collagen deposition and the changes in extracellular matrix contribute to cell loss, myocyte hypertrophy with changes in myosin types, and impaired calcium management, resulting in a prolongation of the membrane potential and the calcium inflow current, hence prolongation of both systole and relaxation.[3]

Age-dependent changes are also observed in the intravascular environment. Increases in fibrinogen, coagulant agents (V, VIII and IX, XIIa), and von Willebrand factor occur without a parallel increase in anticoagulant agents. The phospholipid content of platelets changes, with a concomitant increase in their activity. In addition, with age there is an increase in circulating prothrombotic inflammatory cytokines, especially interleukin-6, which are causative factors in the occurrence of acute coronary syndromes.

The above age-dependent changes create a cardiovascular system that must face an increased pulsatile load and which is unable to increase its output in response to loading conditions. In addition, these changes limit the maximum exercise capacity and reduce functional reserves, thus lowering the threshold for the triggering of symptoms in the presence of cardiovascular diseases, which often occur at advanced ages.

Indeed, cardiovascular diseases are the most common diagnosis and the main cause of death in both men and women aged over 65 years. Hypertension is found in one half to two thirds of individuals over 65 years old, and heart failure is the most common hospital discharge diagnosis. The profile of these common diseases in the elderly differs from that in younger patients. With advancing age, systolic pressure rises and diastolic pressure falls, leading to a progressive increase in pressure difference. Systolic hypertension becomes a more important risk factor for cardiovascular events, especially in women. Heart failure with preserved systolic performance is more common at advanced ages. At ages above 65 years, coronary artery disease is more likely to involve multiple vessels, the main stem included, affecting both sexes equally. Above 80% of cardiovascular deaths occur in individuals aged over 65 years, with about 60% of deaths in patients aged over 75 years.

Some age-dependent cardiovascular changes may be partly, if not completely, reversible. In the elderly, exercise has a beneficial effect on endothelial function, indexes of arterial stiffness, baroreceptor function, and cardiac performance. In many animal models the restriction of caloric intake slows ageing and cardiac changes, while also increasing maximum lifespan. In recent studies in humans, calorie restriction reduced body weight, blood pressure, and risk factors for atherosclerosis, while improving indexes of diastolic function.[4] Pilot studies show that the combination of exercise, stress management, and a specialised diet that reduces LDL cholesterol, also increases the activity of telomerases, which are involved in the slowing of cellular ageing.[5] Drugs such as angiotensin-converting enzyme inhibitors, beta-blockers, antiplatelet agents, and statins have been proved to slow the remodelling and ageing of the cardiovascular system, increasing the quantity and the quality of life, both as a primary measure and in secondary prevention.[6,7]

All the aspirations and achievements of medicine, from Hippocrates to the present day, are summed up in the 90-year-old who stands in front of us. It is right and proper that we should pay him all the attention that he deserves. Both the medical community and the state should listen closely to the needs of individuals of the "third age" and, through a systematic and integrated approach, should ensure that they remain involved and active members of society. We should not acquiesce to the observation of Constantine Cavafy in his poem "An Old Man", with which I shall close this article.

At the noisy end of the café, head bent
over the table, an old man sits alone,
a newspaper in front of him.

Constantine P. Cavafy[1]

1 Translation by Edmund Keeley/Philip Sherrard (http://www.cavafy.com/poems/content.asp?id=39)

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