

## Arterial aging: a brief review

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### Abstract

Aging is associated with changes in arterial wall structure and function that exceed physiological adaptation, with an increased risk of cardiovascular events. The most consistent structural changes are luminal enlargement (dilatation), wall thickening (remodeling), and a reduction of elastic properties. Endothelial dysfunction plays an important role in the functional changes that occur with age. New target therapies to prevent or reverse this process are under evaluation.

**Keywords:** artery, aging, stiffness, endothelium.

### ☞ Introduction

Aging can be defined as all changes that occur gradually in the structure and functions of the human body over time, not the result of a disease, or an accident, ultimately leading to increased probability of death.

Population aging is a worldwide phenomenon. According to the United Nations, the proportion of elderly population will increase on the long term, even in regions where the birth rate is higher than expected. It is expected that in Europe, in 2025, the number of elderly will reach 197.9 million, 78.5% more than in 1975.

Arterial aging is a normal physiological process that develops gradually with age and researchers worldwide are just beginning to understand the complexity of this phenomenon.

Noting that epidemiological studies unequivocally indicate age as an important cardiovascular risk factor there is a particular interest in deciphering the contribution of arterial aging in the development and progress of cardiovascular disease.

Cardiovascular diseases are the leading causes of morbidity, mortality, and disability in industrialized countries, and *American Heart Association* statistics places Romania in the 3<sup>rd</sup> place for death rate from cardiovascular disease.

### ☞ Arterial wall structure

Microscopic, degenerative morphological changes are observed in all components of the arterial wall – a well-organized connective tissue structure composed of cells and matrix fibers arranged in three tunicae: the intima, the media and the adventitia.

#### Tunica intima

Tunica intima has an average thickness of 50–100 μm, without significant variations in size between

the two types of arteries – elastic and muscular –, and consists of vascular endothelium, basal lamina and internal elastic lamina.

*Vascular endothelium* is a “1 kg organ” consisting of about 10 trillion cells arranged in a monolayer of polygonal flat cells that line the luminal surface of all arteries. The average cell size is between 1–2 μm thick and 10–20 μm in diameter. Parietal stress causes variations in shape and size so that in areas where blood flow is laminar and at high velocity, endothelial cells become elongated, spindle-like, with size up to 100 μm.

Cytoplasm is relatively poor in organelles that are located preferentially perinuclear. Common cellular organelles are described as smooth and rough endoplasmic reticulum, mitochondria, ribosomes, lysosomes, Golgi apparatus and a specialized, unique structure, called Weibel–Palade corpuscles.

Weibel–Palade corpuscle is an elongated cytoplasmic formation with the ability to store functional components such as von Willebrand factor, interleukin (IL)-8, endothelin and P-selectin.

Besides the main structural role of controlling molecule, transportation between the vascular wall and the circulating blood the vascular endothelium generates a number of autacoids having an important role in vascular tone regulation [1, 2], homeostasis [3], inflammation [4], the progression of atherosclerosis and angiogenesis [5].

The major endothelium derived autacoid is considered to be nitric oxide. This signaling molecule plays a major role in vascular tone regulation through its vasodilator function, inhibits smooth muscle cell proliferation, leukocyte adhesion and has non-thrombogenic properties.

#### Tunica media

Tunica media is a three-dimensional network of elastin fibers, smooth muscle cells and collagen fibers

[6]. Arteries are classified as *elastic* or *muscular*, according to the relative proportions of these cellular and fibrous components found in the media. In elastic arteries, matrix fibers, in the form of well-defined elastic lamellae and collagen bundles, are abundant and prominent in the media. Muscular arteries contain fewer connective tissue fibers than elastic arteries; smooth muscle cells being the predominant component.

Aortic tunica media structure analysis showed a pattern of relationship between cells and matrix fibers that form a functional unit (elastin fibers, smooth muscle cells, collagen fibers) and is called a lamellar unit. The number of functional units ranges between 53 and 78 [7] and provides adaptation to changes in arterial vascular wall stress.

### **Tunica adventitia**

Tunica adventitia is composed of fibroblasts, elastic fibers, collagen fibers, *vasa vasorum* and nerve structures participating in the regulation of vascular tone and arterial wall nutrition.

Recent studies have demonstrated the role of adventitia in initiation and propagation of inflammation [8], the genesis of atheromatosis, lesional arterial wall repair and identified the presence of progenitor stem cells capable of being converted in smooth muscle cells [9].

### **☞ Arterial remodeling with aging**

Studies have proven both structural and functional changes of arteries exceeding the physiological adaptation that occurs with age. The most consistent changes are luminal enlargement (dilatation), wall thickening (remodeling) and a reduction of elastic properties.

The ageing process is not homogeneous, elastic arteries being more interested by age-associated changes whereas peripheral muscular arteries undergo relatively modest change with age [10]. Considerable research on brachial and radial arteries indicated that diameter increases modestly with ageing and exposure to cardiovascular risk factors like obesity, hypertension, and diabetes mellitus.

Elastic arteries architecture is modified both macro and microscopic. Macroscopic there is progressive dilatation of the lumen, stretching and twisting of the vessel and vessel wall thickening. In a post-mortem study, human aortic diameter was found to be increased by 15–20% in subjects over 65 years compared with younger subjects [11]. Arterial remodeling with age was found to develop independently of high blood pressure. Studies on laboratory animals have shown that lumen expansion is not strictly correlated with increased blood pressure associated with age. Moreover, in laboratory animals, chronic reduction of blood pressure by blocking the renin-angiotensin system did not prevent arterial dilation supporting the hypothesis that arterial remodeling process develops independently [12].

There is experimental support that the sympathetic nervous system activation occurring with human aging may be an important mechanism in arterial remodeling [13].

Arterial wall thickening is the result of smooth muscle cell hypertrophy, collagen synthesis and elastin fragmentation. Wang M *et al.* [14] showed in a morphological analysis on 10 thoracic arteries that diffuse aortic intimal thickness within specimens from the older donors increased by 9-fold compared with those from the younger donors whereas just a 30% increase in medial thickness was seen.

The balance, stability and compliance of the vascular wall are dependent on the contribution of two proteins – collagen and elastin –, and aging is associated with profound changes in the properties of elastin together with stimulation of collagen synthesis.

Qualitative and quantitative changes of elastin fibers include random fiber distribution, increased activity of elastase and increased calcium bound to elastin with aging [15].

It seems that there is a specific increase in arterial wall calcium and phosphorus contents with age, whereas there are no significant increases in most of the other elements, such as sodium, potassium, and magnesium [16].

The development of calcification appears to be specific to human arteries being known that human veins do not develop calcification and animals such as the rat suffer from only very mild arterial calcification with age.

In old arteries, calcification is seen as intimal plaques or located at the level of elastic fibers within the media [17].

Although calcification is correlated with hypertension and atheroma plaques, medial elastocalcinosis independent of atheroma-associated calcification has been demonstrated by Elliot RJ and McGrath LT [15], who selected specimens that were free of plaques and showed that calcium content increased 30- to 40-fold from the age of 20–90 years.

In the past, the interest was focused on studying elastin fibers. Recently more scientific studies have been performed in researching remodeling of collagen. Gudienè D *et al.* [18] studied the collagen network changes in basilar artery with ageing and concluded that quantitative parameters of collagen network – area, number, and perimeter of collagen bundles suffer modifications: an increase of the area and decrease of the number and perimeter of the collagen bundles.

Arterial stiffness is also caused by advanced glycation end products (AGEs), which result from non-enzymatic protein glycation to form irreversible cross-links between long-living proteins such as collagen. AGE-linked collagen is stiffer and less susceptible to hydrolytic turnover [19].

### **☞ Endothelial dysfunction**

The age-associated changes related to the endothelium are also a subject of great interest. It has been demonstrated that endothelial function and its regenerative capacity decline with age.

As a consequence, there is a reduced NO bioavailability [20] and increased expression of endothelin-1 [21] resulting in vasoconstriction, the phenotype turns from

an anti- to a pro-atherosclerotic one, there is an increase in formation of reactive oxygen species [22], increased apoptosis [23], telomere shortening [24] and proinflammatory state.

Morphologically aortic endothelial cells from older donors are fattened and enlarged with an increased number of with polyloid nuclei.

Under normal conditions endothelium cells have a turnover rate estimated at approximately three years. In young arteries, any pathological process initiates endothelial repair (proliferation and differentiation of endothelial precursor cells followed by proliferation and migration of endothelial cells). In contrast, aged arteries have an impaired response known under the term of endothelial senescence.

Endothelial senescence is inversely correlated to telomere length – a new cardiovascular risk marker. Kushner EJ *et al.* [25] tested and demonstrated that telomere length is also reduced in bone marrow circulating-derived endothelial progenitor cells (EPCs) who play a vital role in protecting and regenerating the vascular endothelium through their ability to contribute to re-endothelialization and neovascularization processes at the site of endothelial damage.

Also, ageing and exposure to risk factors such as hypertension, smoking and hyperlipidemia causes endothelial cells to loose their protective role against adhesion of platelets, monocytes or neutrophils.

### ☞ Proinflammatory status and atherosclerosis

The word “atheroma” is a very old one derived from Greek and meaning “groats”. The Leipzig pathologist Marchand, in 1904, appears to be the first to use the term atherosclerosis to designate the degenerative process in inner layer of the arteries. In the last 20 years reports about the inflammatory process that take place within atherosclerotic lesions appeared in scientific literature.

The link between arterial stiffness and atherosclerosis raised numerous assumptions. A number of researchers consider that arterial stiffness is the consequence of atherosclerosis; others think that the rigid arterial wall deprived of the shock-absorbing capacity may predispose to wall damage and atherosclerosis; a third possibility is that both mechanisms apply and that atherosclerosis is not only a consequence of arterial stiffness but may by itself, in advanced stages, also increase arterial stiffness and last but not least that both processes develop independently.

Wang M *et al.* [14] performed a study, which indicated that aging determines cell and matrix proteins to undergo reprogramming in humans, as in animal models, classified as proinflammatory status. Signaling pathway molecules MCP-1 (monocyte chemo-attractant protein) responsible for the migration of monocytes at the site of the lesion into the intima, MMP (matrix metalloproteinases), transforming growth factor (TGF)- $\beta$ 1 and SMC fetal-like are increased in old arteries.

The reduced bioavailability of NO (nitric oxide)

with aging disturbs the anti-inflammatory properties of the endothelium who can no longer inhibit the expression of VCAM-1 (vascular cell adhesion-1), the molecule that binds the specific type of leukocytes found in early human atheroma.

### ☞ Reactive oxygen species

Oxygen molecule plays a double role in human organism: the role of a good molecule participating in cell respiration and the role of a bad molecule which initiates oxidative processes destroying biologically important molecules.

Reactive oxygen species (ROS) are a variety of molecules and free radicals containing oxygen; the term oxidative stress is defined as an imbalance between the production and removal of (ROS) which increases measurable in cells and extracellular milieu.

The vast majority of generated cellular ROS (estimated at approximately 90%) can be traced back to the mitochondria.

For more than a century scientific world suspected that ROS plays an important role in aging process and the pathogenesis of age-related diseases. Up-regulation of pro-oxidants and down-regulation of antioxidants results in an imbalance leading to an increase in ROS, together with consequences on vascular remodeling by vascular smooth muscle cells proliferation, migration and extracellular matrix remodeling [26].

The decrease in endothelial NO bioavailability with aging occurs concurrent with an increase in O<sub>2</sub> production, both in the aorta and in the carotid artery [27].

There are a number of assumptions regarding the decline of endothelium-dependent vasorelaxation with increasing age including increased breakdown of NO due to an augmented production of superoxide anions (O<sup>2-</sup>) [28] or gradual loss of antioxidant capacity [29] which normally provides cellular protection against reactive oxygen species.

### ☞ Can we overcome arterial ageing

It is of great interest to develop new aimed therapies that will slow or even abolish some of the consequences of vascular aging.

One of the paths followed is blocking the formation of ROS by inhibiting NADPH oxidase activity and preventing endothelial senescence [30]. Statins proved to have an antioxidative effect [31] by reduction of circulating LDL cholesterol and circulating markers of oxidation such as F<sub>2</sub>-isoprostane and nitrotyrosine, increase of NO availability [32], augmentation of circulating endothelial progenitors [33] with enhanced functional activity but they also can improve stiffness of arteries in the absence of hyperlipidemia.

Physical activity is associated with low cardiovascular events in many epidemiological studies. The benefits of physical activity include improving endothelial function, reducing vascular oxidative stress by increased activity of endothelial nitric oxide synthase

(eNOS) and extracellular superoxide dismutase [34], which in turn could exert beneficial vascular effects. Daily aerobic exercise or walking was also found to improve carotid artery compliance in previously sedentary middle-aged/older men.

Resveratrol is a polyphenolic compound in red wine that has anti-oxidant and cardioprotective effects in animal models by inhibiting foam cell formation, one of the most important steps in atherosclerosis, as well as ROS production [35, 36].

One of the greatest hopes in anti-aging therapy is the study of endothelial progenitors that appear to be involved in repair and angiogenesis of ischemic tissues.

In the *Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction* (TOPCARE-AMI) [37] trial, patients received infusions of bone marrow derived mononuclear cells or EPCs approximately four days after myocardial infarction. After 12 months, patients exhibited improved ejection fraction and end-systolic volumes, indicating improved cardiac function.

### ☒ Conclusions and future perspectives

Aging is characterized by structural and functional changes in the arteries, with increased risk of cardiovascular events. The cellular and molecular mechanisms underlying age-associated changes of the vessels have not been fully elucidated. Understanding these processes can guide pharmacological therapies, which prevent arterial stiffness, and improve cardiovascular morbidity and mortality.

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*Received: December 20<sup>th</sup>, 2011*

*Accepted: August 6<sup>th</sup>, 2012*