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Maladaptive neuropathological syndrome of blood vessel aging

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This article discusses the relationship between maladaptation and blood vessel aging. The work shows that upright posture created an additional load on the circulatory system, and the lifestyle of a modern human is an additional risk factor of cardiovascular diseases. It has been suggested that a disorder of the nervous regulation of vascular tone is the main etiopathogenetic mechanism of morphofunctional changes in blood vessels and their aging. We discussed the statute that vascular reactions in humans is based on the formation of a maladaptive circuit in the cerebral cortex, consisting of a matrix of motor, sensory and associative cortical neurons involved in the maladaptive process. This hypothesis is based on the fact that any irritations entering the cerebral cortex from the periphery (thermal, pain, and others) cause cortical-vascular reflex reactions that change their tonic activity. Based on this principle, a model of vascular aging is further constructed, which is based on the maladaptive damage to all layers of the vascular wall (intima, media and adventitia). The opinion is expressed about the need for early diagnosis and prevention of vascular disorders to maintain human health. In conclusion, it is concluded that if the age of a person is really determined by the age of his blood vessels, then in order to achieve active longevity it is necessary to normalize the relationship in the adaptation-maladaptation-environment. Detailed study of hypertrophy and calcification of blood vessels is needed, since aging always reveals vascular wall thickening and stiffness increase.

Key words: cardiovascular diseases, maladaptation, vascular tone, vascular aging, morphofunctional changes, prevention of vascular aging.

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There is a perception that one of the main reasons for the increase in the prevalence of cardiovascular diseases (CVDs) is the steady ageing of the population. Blood vessels (BV) of the human body are also vulnerable to aging. It is the age-related changes in blood vessels that are an important risk factor for CVDs. Morphofunctional changes in the vascular wall developing with age contribute to the beginning and progression of CVDs.

The nature of CVDs is complex and still not clear enough, because the mechanisms of BV aging are quite complex and diverse. But every year vascular biology and medicine reveals new facts that allow a deeper understanding of the molecular mechanisms of vascular wall damage and on this basis to prevent or minimize the early BV aging.

Cardiology attaches great importance to the development of new concepts and pathophysiological models for a better understanding of cardiovascular risks, early diagnosis, treatment, reduction of morbidity and mortality from cardiovascular pathology. Many studies are now aimed at finding etiological factors that accelerate the aging process of BV. Important role in the disturbance of systemic and peripheral blood circulation is played by mechanisms of vascular tone regulation, which can be easily disturbed in everyday life of people. It is not a secret that every year the number of different kinds of environmental factors that disrupt the neurohumoral regulation of vascular tone and thus trigger the molecular mechanisms of BV aging increases [1]. The neuropathological syndrome of BV aging developing in a human being is, on the one hand, caused by the disturbance of vascular tone regulation, and, on the other hand, by the damage of all layers of the vascular wall (adventitia, media, and intima) due to morphological changes.

The aim of this review is to acquaint the reader with the main mechanisms of the occurrence and development of a maladaptive neuropathological syndrome of BV aging in humans.

Maladaptive disorders of vascular tone during aging

Maladaptation, being a general pre-pathological (interjacent) state of an organism, triggers numerous mechanisms leading to the degradation of biological systems and the development of morphofunctional changes in organs and systems, including BV [2]. Currently, it is believed that the main mechanisms of vascular aging associated with the adaptation process are oxidative stress, endothelial dysfunction, chronic inflammation, apoptosis of endothelial cells, impaired function of endothelial progenitor cells, age-related dysregulation of vascular system [3].

An occlusion test can be used to detect dysregulation disorders of microcirculation and vascular tone, which reveals a decrease in the reserve of capillary blood flow, a change in the reactivity of microcirculatory vessel, and an increase in stagnation in the microvasculature [4]. The biochemical component of vascular tone assessing can be the detection of Rho-associated protein kinase activity in smooth muscles and vascular endothelium, which is involved in the regulation of vascular tone both in normal state and in vascular disorders [5]. At the same time, it is known that the arginase enzyme promotes microvascular endothelial dysfunction in obesity in humans.

However, its effect significantly decreases with age due to a higher level of vascular oxidative stress. Thus, it is possible that obesity is accompanied by accelerated microcirculatory vessels' remodeling, which is associated with the arginase content in the vessel wall [6]. But one cannot ignore the fact that in the group of young patients with stiff vessels, compared with people with elastic vessels, a higher level of total cholesterol and low-density lipoprotein cholesterol was detected [7].

It is worth noting one more interesting fact related to vascular tone maintaining, namely, the effect of endothelial zinc (Zn) homeostasis on this process. The pathways of the influence of Zn as a biogenic element and nitric oxide (NO) in the human body are closely related. The labile chemical element Zn can mediate important functions of NO, including vascular cytoprotection and vasodilation [8].

The situation is somewhat different with the regulation of vascular tone during aging in patients with cardiovascular pathologies than without it. An analysis of the literature shows that in patients with arterial hypertension, pronounced microcirculatory disorders associated with changes in vascular tone and blood rheological properties are noted. This, in turn, determines the value of the total peripheral vascular resistance [9]. It was also found that increasing stiffness of elastic-type vessels in young patients is associated with an increase in systolic blood pressure, and in muscle-type vessels, with an increase in diastolic blood pressure [10]. Arterial stiffness increases with age and increases the risk of CVDs. However, functional disorders of the elastic properties of the carotid artery walls can occur even before the formation of structural changes and can be detected by ultrasound imaging even before the onset of CVD symptoms [11].

Vascular stiffness, determined by pulse wave velocity in the carotid and femoral arteries, is now used to predict cardiovascular risk and assess vascular tone disorders [12].

However, it has been found that the severity of autonomic cardiovascular dysfunction during orthostatic stress among patients does not depend on tolerance to hypoxia [13]. Violation of vascular signaling processes (for example, decreased bioavailability of nitric oxide) is usually called endothelial dysfunction, which is a recognized risk factor for CVD [14].

In older people, endothelial dysfunction occurs as an altered endothelial ability to regulate hemostasis, vascular tone and cell permeability. These changes enhance the procoagulant status that develops with aging and emphasize the key role of endothelium in the development of thrombosis during aging [15]. Gender differences in hemodynamic values such as vascular stiffness, elastic modulus, and pulse wave velocity are not excluded. This can give general ideas about the treatment strategy regarding developing drug therapy for different sexes [16].

There is an opinion that the hemodynamic response of the cardiovascular system varies significantly with healthy aging and depends on the level of arterial oxygen tension [17]. Thus, it should be recognized that aging worsens endothelial function both in the cerebral arteries and in parenchymal arterioles, mainly by affecting the endothelial regulation of vascular tone, which depends on nitric oxide [18]. Endothelial aging is associated with impaired renal artery function, which is partially characterized by arterial stiffness and reduced vasodilating ability due to excessive formation of reactive oxygen species, resulting in the so-called endothelial dysfunction [19, 20].

Neurophysiological associations

To explain the processes of altered regulation of the cardiovascular system, it is proposed to introduce the following concept. A peculiar matrix of nerve networks in the cerebral cortex and subcortex forms a "maladaptive contour". Such a pathodynamic complex includes neurons of the motor, sensory, and associative zones of the cortex, since they have a strong (constrictive and dilative) effect on the vascular lumen. Supporting role in this process is played by neurons of the frontal and parietal lobes. The maladaptive pathodynamic contour along the descending paths directly affects the pressor and depressor parts of the hypothalamus and the same parts of the underlying vasomotor center of the medulla oblongata, causing a change in the functions of neurons of the spinal vasomotor center and BV.

Nevertheless, it can be concluded that a neuropathological complex of maladaptive disorders of vascular tone is formed in the structures of the central nervous system, which manifests itself in humans in certain life situations and with aging. The disintegration of the maladaptive contour, which consists of hyperactive neurons and nerve centers involved in the maladaptive process, under the influence of treatment, rehabilitation measures and pharmacotherapy leads to normalization of the hemostasis, disappearance of pathological cortical-vascular reactions, normalization of arterial pressure, and the subsidence of psychological, physical and functional manifestations of maladaptation.

Maladaptive damage to the vascular wall during aging

Long-term maladaptive disorders of vascular tone over time lead to morphological changes in the vessels and impaired function. It was shown [21] that BV aging is accompanied by a violation of the state and function of its three main layers: intima, media, and adventitia. With age, each of these cell layers undergoes complex changes, leading to a total of two consequences — a thickening of the vascular wall and an increase in its stiffness. These two components of pathogenesis create an unfavorable basis for vascular aging and clinical manifestations of CVD [22].

The scientific data discusses the fact that accelerated aging of BV is associated with their calcification, which directly affects the higher mental functions of a person. For example, calcification of the carotid artery has a significant correlation with cognitive impairment, and intracranial calcification of BV is associated with extensive changes in the white matter and causes pronounced neuropsychiatric symptoms [23-25]. Nevertheless, there is evidence that the biological age of the arteries (stiffness and elasticity) is interrelated with risk factors for atherothrombosis. Premature aging of BV is associated not only with disruption of glucose utilization by cells, but also with initial manifestations of chronic inflammation of the arterial wall and a tendency to thrombosis [26].

It should be noted that an increase in arterial stiffness is currently considered to be a link between diabetes and a high risk of CVD. Insulin resistance is an important factor in the formation of vascular aging processes [27, 28]. BV aging occurs intensively in the menopausal period, which is often characterized by endothelial dysfunction and arterial stiffness, which is the main risk factor for CVD. In this case, the endothelial function of the vessels progressively decreases, and the acceleration of vascular aging can be associated with the loss of the vasodilating, antioxidant, anti-inflammatory and antiproliferative effects of estradiol on the vessel wall [29]. It has been shown that in obese individuals respiratory disturbances in sleep can be a risk factor for early vascular aging [30].

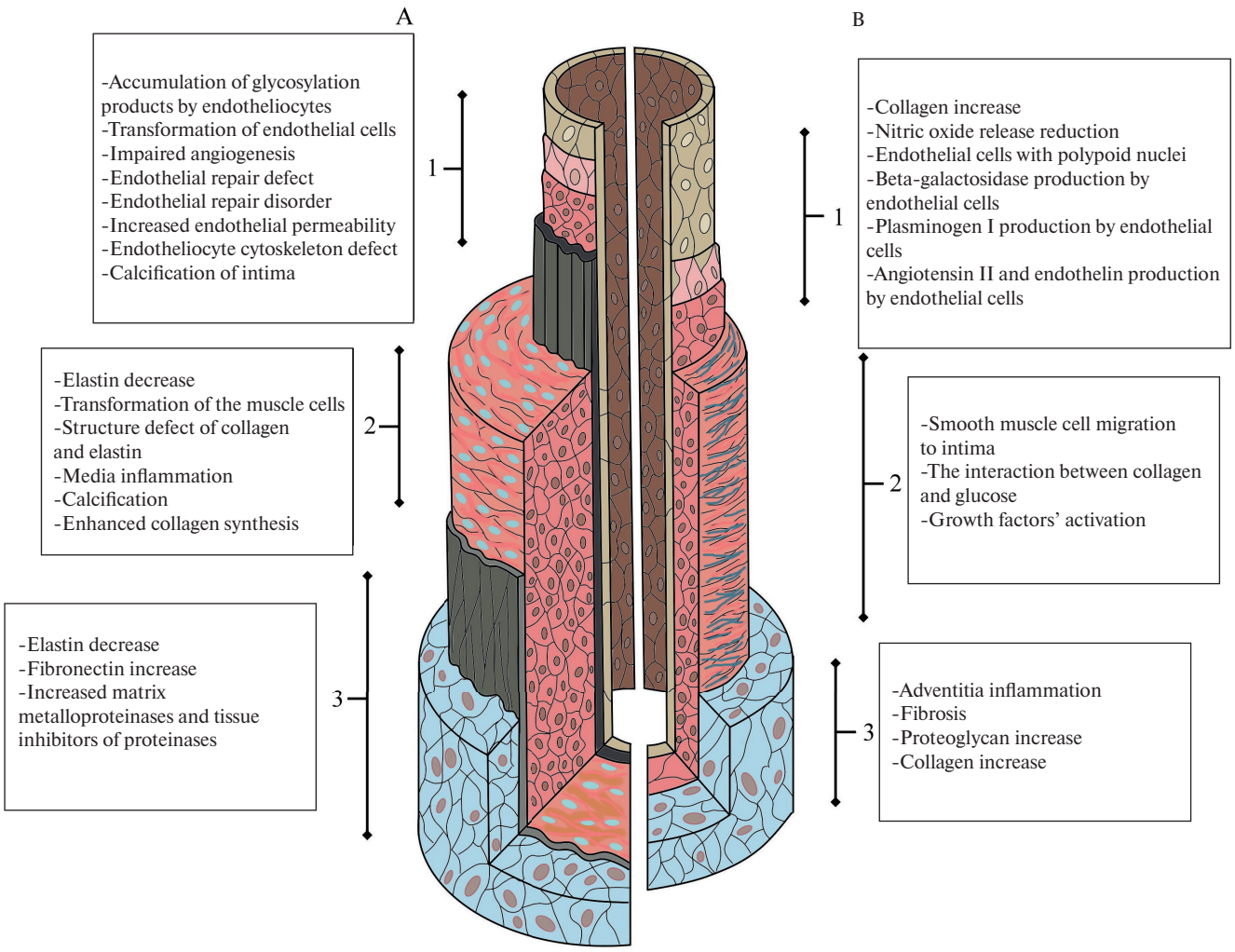

Fig. 1. The main pathogenetic mechanisms of vascular aging: A — artery. B — vein. 1 — innermost layer (tunica intima); 2 — middle layer (tunica media); 3 — outermost layer (tunica adventitia).

It is possible that in patients with arterial hypertension, in combination with overweight and obesity, an increase in cerebral and hemodynamic pathologies is accompanied by anxiety-depressive disorders [31]. At the same time, the presence of such an additional risk factor as smoking leads to the occurrence and progression of changes in the artery wall even in apparently healthy humans [32]. Smoking can also have a negative effect on vascular aging in a group of patients after cancer-related radiation therapy [33].

Thus, vascular remodeling during aging is an adaptation process, including structural and functional transformations of the vascular wall that occur in diseases, injuries, and ultimately lead to damage of target organs [34]. Arterial hypertension causes remodeling of vessels of all types already in the adult period of life, while increasing the integral biological age of the patient [35].

With the aging and development of hypertension, endothelium, vascular wall and adventitia undergo functional and structural changes. The endothelial function of BV in this case is impaired, and the vascular wall is thickened. The extracellular adventitia matrix undergoes remodeling with increased collagen deposition, a decrease in the elastin content and an increase in the number of inflammatory cells. These processes contribute to vascular fibrosis and increase vascular stiffness [36].

Study of the volume of arterial and venous vessels of the renal cortex and medulla revealed the morphological changes during aging, which are characterized as nephrosclerosis [37]. It should be noted that among the signs of vascular aging, activation of the renin-angiotensin-aldosterone system as the main source of chronic inflammation and oxidative stress is being

considered [38]. Not without reason we can say that the precursor of the miR-34a family of microRNA effector molecules is associated with vascular calcification and its stimulation. This, in turn, includes the transdifferentiation of vascular smooth muscle cells caused by aging, inhibiting cell proliferation and, thus, leading to mineralization of the arterial wall [39]. Therefore, vascular smooth muscle cells play a crucial role in vascular aging and the formation of aneurysm of the ascending thoracic aorta. The occurrence of aneurysm is characterized by an increase in the permeability of the vascular wall, leading to transmural migration of plasma proteins, which can interact with vascular smooth muscle cells and extracellular matrix components [40].

The result of pathological processes in the vessels is an increase of pulse wave velocity [41]. Summarizing the available data on the BV aging issue, we note that maladaptation of the body plays an important role in the damage to all layers of the vascular wall. Being a general biological systemic process [42], it inevitably leads to malregulation disorders of vascular tone, persistent distention or constriction of BV, and numerous metabolic disturbances in endothelial, smooth muscle and adventitia cells already appear. (Fig. 1).

Thus, with BV aging, malregulation disorders are primary, and then changes in the vascular wall already occur. That is because vegetovascular disorders can be observed in the early stages of postnatal ontogenesis (children, adolescents and young people). At the later stages of ontogenetic development (in adult, senile and elderly age), irreversible structural changes in the vascular wall already occur and lead to its dysfunction.

Diagnostics, prevention and correction of vascular disorders

Based on the sphygmography method with the of vascular age determination, a screening examination of the population can be carried out for early detection of changes in the vascular wall [43].

The concept of "vascular age" analyzes the possibility of using the pulse wave velocity and central aortic pressure as the stiffness markers of main elastic-type arteries of the depending on the chronological age is analyzed [44]. Depending on age and gender, if necessary, longitudinal movements of the intima-media complex of the common carotid artery can be detected [45].

The use of transspinal micropolarization for the treatment of impaired brain systems associated with the regulation of vascular tone is also justified [46]. The possibility of aging markers using such as myocardial hypertrophy and left ventricular diastolic dysfunction as cardiovascular markers of aging has been proven. In this regard, the necessity of assessing the rate of vascular aging was substantiated in order to identify young patients with a high risk of myocardial infarction [47].

Experimental studies indicate that millimeter-wave electromagnetic radiation exhibits properties. By regulating the exposure of a culture of vascular endothelial cells, we can activate the expression of signaling molecules, the synthesis of which underlies endothelial dysfunction during aging [48]. Other studies have shown that multipotent mesenchymal stromal adipose tissue cells can stimulate angiogenesis [49]. There is also an opinion that mediators of the sympathetic nervous system (adrenaline and noradrenaline) protect vascular cells from the damaging effects of nitrogen dioxide formed during hypoxia, ischemia, inflammatory and other pathological processes [50].

In addition, it was found that in the late stages of postnatal ontogenesis, pharmacotherapy of vascular diseases plays an important role. Data on the positive effect of angiotensin-converting enzyme inhibitors as geroprotectors on the vascular wall are given [51]. The vasoprotective activity of indapamide has been shown [52]. Meantime, determination of the features of microcirculatory disorders in patients in the recovery period after ischemic stroke allows us to recommend drugs that improve the flow of arterial blood to tissues, reduce vascular spasm, as well as massage, physiotherapy, reflexology, physiotherapy exercises [53]. Adding melatonin to the traditional therapy of metabolic syndrome in patients with sleep disorders improves the function of endothelial cells, reduces vascular stiffness and normalizes blood pressure [54]. It was also shown that combinative antihypertensive therapy with a calcium antagonist and an angiotensin-converting enzyme inhibitor increases the estimated vascular age of patients by an average of nine years [55, 56]. To protect the endothelium, herbal products rich in polyphenols are studied [57, 58].

In this study, it was shown that the inclusion of aerobic training, strength gymnastics and darsonvalization in the rehabilitation complex provides the normalization of heart rate and blood pressure. It is known that at the same time stress of adaptation mechanisms decreases, sympathetic effects on the heart and blood vessels weaken, and vascular tone normalizes [59]. These data are confirmed by studies that indicate improvement in cerebral circulation and cognitive functions under the influence of aerobic exercise [60].

Thus, it can be established that “vascular age” is a new parameter of health and, ultimately, an integral parameter of damage to internal organs (heart, brain

and kidneys). And arterial stiffness is the most commonly used measure of BV aging. It is known that over time there is a steady increase in arterial stiffness with an average blood speed of 0,2 to 0,7 m/s. Therefore, arterial stiffness is very important for vascular aging assessing [61].

Conclusion

Human health is determined by the age of his blood vessels — that is the conclusion that can be drawn by summarizing the presented data. Such an opinion is currently coming to specialists dealing with the problem of aging and longevity. Today, preventive measures aimed at preventing premature BV aging are at the forefront. Healthy vessels are needed to maintain a person's active longevity.

However, we are becoming increasingly convinced that the biosocial nature of human being, civilization, the nutrition and lifestyle of modern man have a negative impact on BV. Preserving healthy vessels and prolonging human life is the task of gerontology and preventive medicine in the future.

One of the directions of such work is the normalization of relationships in the system of adaptation-maladaptation-environment. Indeed, in the modern world the number of stressful situations and borderline states of mental maladaptation is growing, and as we know, any neuropsychiatric disorder will certainly affect the BV tone. It is maladaptive disorders of neurohumoral regulation of vascular tone that are the root cause of morphological changes in the vascular wall. It should be emphasized that a clear sign of vascular aging is a thickening of the vascular wall and an increase in its rigidity. True BV hypertrophy and their calcification develop as a result of impaired neurohumoral regulation of functions. And then, with the loss of regulatory effects on the vessels, metabolic disturbance, their calcification, atherosclerosis and progressive dysfunction occur. In any case, it seems that the phenomenon of compensatory BV hypertrophy associated with calcification should be carefully studied.

Conflicts of Interest: nothing to declare.

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