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EVA and SUPERNOVA concepts of vascular aging: ongoing research on damaging and protective risk factors

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Abstract

Regarding prevention of cardiometabolic diseases, we often rely on the concepts of risk and disease, rather than the possibility of prevention. The concept of "vascular age" is developed to assess the biological state of arteries and to present cardiovascular risk in years for better understanding by the doctor and patient. Early vascular aging (EVA) syndrome has been studied for more than 10 years to determine the optimal diagnostic criteria and treatment approaches. In 2019, leading experts in the area of vascular stiffness suggested the opposite concept of supernomal vascular aging (SUPERNOVA), in which patients have extremely low vascular stiffness rates for their age and gender. This review discusses new data about factors that accelerate or slow vascular aging.

Key words: arterial stiffness, SUPERNOVA, EVA, hypertension

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Сосудистое старение в концепциях EVA и SUPERNOVA: непрерывный поиск повреждающих и протективных факторов

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Резюме

В вопросах профилактики кардиометаболических заболеваний мы чаще всего опираемся на понятия риска и болезни, а не возможности сохранения здоровья. Концепция «сосудистого возраста» разработана для оценки биологического состояния артерий и выражения сердечно-сосудистого риска в годах для лучшего понимания врачом и пациентом. Преждевременное старение сосудов (на английском early vascular aging (EVA) синдром) изучается более 10 лет в рамках определения оптимальных критериев диагностики и терапевтических подходов лечения. В 2019 году ведущие эксперты в области изучения сосудистой жесткости предложили противоположную концепцию супернормального сосудистого старения (SUPERNOVA), при которой у пациентов наблюдаются чрезвычайно низкие показатели сосудистой жесткости для их возраста и пола. В настоящем обзоре обсуждаются новые данные о факторах, которые ускоряют или замедляют сосудистое старение.

Ключевые слова: сосудистая жесткость, раннее сосудистое старение, супернормальное сосудистое старение, артериальная гипертензия

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Introduction

Regarding prevention of cardiometabolic diseases, we often rely on the concepts of risk and disease, rather than the possibility of prevention. People usually seek medical help when serious complications occur. Medical professionals do not have enough time and opportunities to provide information to those who do not need medical help. Even if someone goes to see a doctor in a timely manner, recommendations are not followed properly or implemented selectively. We should recognize that part of the low compliance is due to the patient's lack of understanding the risk of disease and/or the need to start treatment. Present risk scales are far from being perfect, so we are always in search for new ways to improve existing ones and identify new risk factors.

Age is an important predictor of cardiovascular risk. In addition, the burden of age-related diseases is increasing due to rised life expectancy. Depending on the ratio of indicators of chronological and

biological age, there is a distinction between premature vascular aging (early vascular aging (EVA) syndrome) and normal (healthy) vascular aging [1]. The concept of "vascular age" is designed to assess the biological state of arteries and express cardiovascular risk in years for better understanding by medical professionals and patients. There are numerous methods for estimating biological age, which can be divided into "value-based" and "risk-based" approaches [2]. Each approach has its disadvantages and the search for the perfect one still continues. According to the results of our comparative study, in a sample of low-risk individuals the instrumental and calculating approaches of assessing vascular age had low consistency. Assessing the virtual load of risk factors on arteries appeared to be more sensitive to detecting premature aging as it also required less financial and organizational efforts [3].

EVA syndrome has been studied for more than 10 years to determine diagnostic criteria and treatment approaches. In patients with EVA syndrome the ability to repair vascular damage in response to mechanical and metabolic/oxidative/chemical stress is impaired. Arterial stiffness shows both the influence of all risk factors as well as the susceptibility to these influencing factors and the duration of exposure. According to the results of our data analysis from a population sample of residents of Saint Petersburg, EVA syndrome was detected in 3 to 17% of participants, depending on the methods of assessment (low consistency was registered between methods). Predictors of accelerated vascular aging were hypertension, hypertriglyceridemia, and diabetes [4].

Of course, hypertension is one of the most significant factors of vascular aging. In HYPERION trial patients with hypertension biological age exceeded chronological age by an average of 17.6 years in men, and 13.4 years in women [5].

In 2019, leading experts in the field of arterial stiffness research confirmed statement that arterial stiffness is the best indicator of the combined effect of known and unknown risk factors for arterial damage. Terms «EVA» and «SUPERNOVA» (supernormal vascular aging), describing very high and very low arterial stiffness were suggested. Individuals with SUPERNOVA have extremely low vascular stiffness rates for their age and gender. It can be assumed that for some reason exposure to cardiovascular risk factors does not lead to subclinical organ damage and cardiovascular complications [6].

This review focuses on discussing the new data on damaging and protective factors that affect vascular wall.

Genetic and epigenetic markers

One of the topics discussed over the past decade is the influence of telomere length on cardiovascular system. Telomeres are repetitive non-coding sequences of DNA (TTAGGG) located at both ends of each chromosome and are protecting the ends of chromosomes. During each cell division telomeres become shorter. Therefore, the length of leukocyte telomeres has been proposed as a biomarker of aging [7]. Researchers can't agree on whether telomere length is a risk marker or determining risk factor. Numerous studies have identified links between short telomeres and hypertension, diabetes, atherosclerosis, coronary heart disease and stroke as well as with pulse pressure. Contradictory but sometimes paradoxical results can be explained by differences in methodology and populations studied, but probably also by the complexity of telomere biology [8].

Mario Laganovic and collaborators (2014) in their study found out that young men born with intrauterine growth restriction (IUGR) had significantly longer telomeres (the average telomere length was 42% longer) than young men born after normal pregnancy [9]. Some molecular mechanisms may explain the paradoxical detection of longer telomeres in men born with IUGR (for example, compensatory telomerase activation, telomere methylation and histone acetylation) [10]. If we assume that this trend will be the same in the following years, we can expect that the telomere length of men born with IUGR will be shorter in their third or fourth decade of life than in the control group. This can lead to early onset of various diseases associated with aging including cardiovascular diseases (CVD) [11].

A recent prospective study by S. Masi and collaborators (2014) showed that faster rate of telomere shortening was associated with an increase in thickness of the intima-media complex of carotid arteries, regardless of common-known risk factors for CVD. This leads to the hypothesis that telomere shortening provides cellular and genetic link with vascular aging [12].

Barry J. McDonnell and collaborators (2013) showed that age changes the association between telomere length and pulse wave velocity (PWV) in healthy individuals (reverse association present young individuals and positive association present

in the elderly ones) [13]. These data suggest that the links between cellular and vascular aging reflect the complex interaction between genetic and environmental factors that we are exposed to throughout life. However, the links between cellular and vascular aging are not clear enough and deserve further study.

Special attention is paid to the study of complex mechanisms regulated by epigenetics for understanding optimal mechanobiology and limiting the development of CVD. Newly discovered genetic variant in the cib2 gene (calcium and integrin-binding protein-2) associated with hypomethylation of the promoter region was detected in the British Twins UK cohort. This variant increases the expression of cib2-protein that regulates intracellular calcium levels and reduces PWV [14].

V. L. Herrera and collaborators (2014) demonstrated the effect of sodium on arterial stiffness in stroke-prone rats. The authors showed that increased level of sodium leads to increase in the level of an epigenetic regulator that promotes DNA methylation and histone modification in all layers of the vascular wall, which leads to an increase in PWV and subsequent development of hypertension [15].

IY. Z. Wan and collaborators (2014) demonstrated that inhibition of SIRT1 (Silent Information Regulator — 1) expression of PAI-1 (plasminogen activator inhibitor-1) works against endothelial cell replication associated with vascular aging and the development of atherosclerosis. The authors noted that overexpression of SIRT1 reversed the increased expression of PAI-1 in the aorta of old mice accompanied by improved endothelial function and decreased arterial stiffness [16].

It is known that vascular smooth muscle cells plasticity (VSMCs) plays an important role in increasing blood pressure (BP) not only by regulating the interaction of actomyosin for contraction but also by mediating mechanotransduction in the homeostasis of the cell-extracellular matrix. It is also very important for physiology of normal and early vascular aging. The contribution of epigenetic processes to the degree of plasticity (stiffness) of VSMCs was clearly established. Transcription factor KLF4 (Kruppel-like factor 4 / Krüppel-like factor 4) and phosphorylated ETS-like (E 26 transformation-specific or E-twenty-six) transcription factor-1 co-recruit HDAC 2 (histone deacetylase) which encodes the sm22a VSMCs differentiation marker (smooth muscle-specific protein SM22alpha). Migration of differentiated VSMCs to adventitia leads to the formation of resident pluripotent progenitor cells. Maintenance of the precursor phenotype depends on KLF4 [17]. It can be assumed that this physiological reprogramming of the VSMCs in situ could be critical in subjects with SUPERNOVA.

Behavioral risk factors

Nutrition

Chronic calorie restriction without eating disorders is known to have a positive effect on stem cell function, cell aging, inflammation and metabolism. According to some studies, nutrition also affects the stiffness of aorta. Finnish study (945 people) demonstrated that the presence of metabolic syndrome in childhood and adolescence predicts increases arterial stiffness in adulthood. Conversely, the improvement of metabolic parameters in children is associated with decrease in arterial rigidity during adulthood [18].

Feeding mice with foods high in sucrose and fat leads to development of oxidative stress, increased regulation of proinflammatory mediators and a decrease in the bioavailability of NO in the aortic wall for 2 months. Reduced NO bioavailability was associated with increased activity of transglutaminase 2-NO-sensitive enzyme [19], which leds to increased cross-linking of structural proteins in aortic wall. It is important to note that when the mice were brought back to a normal diet, their weight returned to the previous level within 2 months. This was also associated with decrease (to normal range) in the speed of the aortic pulse wave and BP level. The results obtained in this model of dietary hypertension and vascular inflammation are very relevant in the sense of the obesity epidemic and emphasize the contribution of aortic pathology to pathogenesis of hypertension.

Recent evidence suggests that dietary supplements with vitamin K can help to reduce arterial stiffness. Vitamin K-dependent proteins are associated with vascular stiffness and vascular calcification. J. S. Lees and collaborators (2019) conducted a meta-analysis of 27 large studies and concluded that taking vitamin K supplements significantly reduced vascular calcification, but had no effect on vascular stiffness. The level of vitamin K-dependent proteins was associated with the achievement of the end point of CVD or mortality. However, findings were limited to a small number of studies that were characterized by significant heterogeneity [20]. In another meta-analysis, H. G. Chen and collaborators also noted that higher vitamin K intake is associated with a

lower risk of CHD and higher plasma concentrations of desphospho-uncarboxylated matrix Gla-protein (vitamin K-dependent protein) are associated with an increased risk of all-cause mortality and CVD [21].

Excessive intake of fat in the diet appears to disrupt the intestinal barrier function and cause endotoxemia. A number of bacterial components can activate innate and adaptive immune responses, which can also cause changes in glucose and lipid metabolism and contribute to the development of obesity and hypertension with pro-atherosclerotic effect [22]. Recently published paper by C. Menni and collaborators (2018) provides important evidence for the relationship between the composition of the intestinal microbiome and arterial stiffness [23]. The authors studied a sample of 617 middle aged women registered in the Twins UK registry who had a significant association between PWV and the composition of the intestinal microbiome after adjusting for four categories of mixed factors: 1 — lifestyle risk factors; 2 — common-known CVD risk factors, such as a 10-year risk score for ASCVD (atherosclerotic cardiovascular disease); 3 — inflammatory markers; and 4 — metabolic factors. The authors noted that microbiome factors explain 4.1–8.4% of the PWV variance, whereas the ASCVD score, HOMA-IR index and visceral fat taken together explain 5.51–11.24%. These results were obtained after adjusting for age, average BP and BMI (body mass index).

Cristina Menni and collaborators (2018) also found that arterial stiffness is negatively correlated with the abundance of Ruminococcaceae bacteria (it produces butyrate, an excess of which in mice is associated with lower endotoxemia) [23]. It is known that experimentally induced acute endotoxemia increases the production of inflammatory cytokines and causes endothelial dysfunction in humans; chronic endotoxemia is associated with metabolic syndrome [24]. It is well known that obesity, especially abdominal obesity, and insulin resistance correlate with less microbiome diversity [25].

Physical activity

Mechanisms underlying the protective effect of regular exercise on CVD may probably include maintaining arterial elasticity or reducing arterial stiffness [26]. In those living a sedentary lifestyle, arterial stiffness increases with age despite good health. It is noted that regular aerobic exercise can reduce arterial stiffness in previously sedentary, but healthy middle-aged and elderly men, as well as in almost healthy postmenopausal women. Moreover, this does not depend on changes in body weight, blood pressure, risk factors for coronary heart disease or the state of the cardiovascular system. More importantly, these effects can be achieved with moderate physical activity, which can be performed by most of the population. There is evidence that swimming can effectively reduce the stiffness of central arteries during menopause in female patients with essential hypertension [27].

A study in mice reported a small effect of regular exercise on the total collagen content in the carotid arteries, but there was also significant decrease in the density of collagen type I and III [28]. Thus, qualitative changes in arterial wall collagen occur with regular aerobic exercise.

The effect of aerobic training on arterial stiffness is more significant in the central (elastic type) than in the peripheral (muscular type) arteries [29]. It is reasonable to assume that mechanical factors could interact with functional elements to modulate arterial stiffness, since collateral arterial stretching is significantly greater in the central arteries compared to peripheral. This characteristic of arterial wall underlies the dependence of arterial stiffness on heart rate in vivo, since the influence of heart rate is more expressed in elastic than in muscular arteries. Indeed, vascular smooth muscle cells are considered as the main regulatory factors of arterial rigidity [30].

Some of health organizations recommend weight training as an important part of physical activity for prevention and rehabilitation programs. It turned out that several months of such training significantly increased arterial stiffness in healthy men [31]. It should be noted that increased vascular stiffness during training with weights was not observed in older people with already increased arterial stiffness if the exercise program corresponded to the guidelines established by the American heart Association [32]. Healthy postmenopausal women doing mixed training for 3 months for endurance and resistance showed a tendency to decrease arterial stiffness [33].

The question of whether the effects of regular aerobic exercise can be additive to the effects of other popular lifestyle modifications (such as sodium restriction, the Mediterranean diet) has not been widely considered. In clinical trials, regular intake of lactotripeptide (biologically active antihypertensive peptides found in dairy products) and regular aerobic exercises significantly reduced carotid artery stiffness in postmenopausal women [34].

Smoking

Smoking is considered to be one of the most significant factors of vascular aging. Park W. Park and collaborators (2014) indicated increased arterial stiffness in chronic smokers, especially in those who live a sedentary lifestyle [35]. It is currently becoming relevant to recognize the harm of electronic cigarettes. Research in this area is not always objective (possibly because of the influence of the tobacco industry) and requires a long time to obtain valid results. There is evidence that when switching from smoking regular cigarettes to using e-cigarettes (smokers ≥ 18 years old who smoked ≥ 15 cigarettes a day for ≥ 2 years, without CVD), there was an improvement in endothelial function and vascular stiffness within a month after quitting tobacco cigarettes, especially among women [36].

However, most studies demonstrate negative impact of electronic nicotine delivery systems. So, K. F. Frantzen and collaborators (2018) conducted a randomized cross-study with participants who were divided into groups depending on the use of regular cigarettes, e-cigarettes with or without nicotine (eGo-T CE4 vaporizer). Peripheral SBP increased significantly at 45th minute after vaporizing the nicotine-containing liquid and at 15th minute after smoking a regular cigarette. In addition, heart rate remained elevated approximately 45 minutes after vaping an electronic cigarette with nicotine-containing liquid and for the first 30 minutes after smoking a regular cigarette, in contrast to the control group. The increase in PWV did not depend on the average BP, as well as heart rate in the groups of participants using e-cigarettes or regular cigarettes [37]. According to another trial in which authors studied the effect of e-cigarettes on vascular function among young healthy participants, there were no significant changes in heart rate, SBP and DBP, endothelial function and arterial stiffness [38].

We should not put aside negative effects of passive smoking. According to study on the effect of e-cigarette aerosol without nicotine for 6 months on the vascular function of young non-smokers, there was slight but significant increase in PWV [39].

S. Xue and collaborators (2019) in a recent trial studied the effect of nicotine replacement therapy (NRT) on vascular function. After 3 months of NRT, endothelial function, arterial stiffness and markers of inflammation significantly improved in participants who abstained from smoking completely. These indicators remained unchanged for those who did smoke cigarettes. After 12 months of follow-up, participants who abstained from smoking had additional improvements in endothelial function, arterial stiffness and markers of inflammation. Among participants who continued smoking, parameters listed above deteriorated [40].

Hookah smoking is rapidly gaining popularity around the world. M. Rezk-Hanna and collaborators (2018) conducted a study among 48 young healthy people who smoked only hookah. Hookah smoking was accompanied by increase in heart rate, brachial artery BP, PWV and aortic augmentation index against the background of increase in plasma nicotine concentration. Thus, one session of hookah smoking in young people causes significant increase in arterial stiffness to the extent comparable to smoking cigarettes [41].

The effect of smoking and alcohol intake on arterial stiffness in adolescence was examined in 1,266 adolescent participants (425 male and 841 female) in ALSPAC trial. There were no differences in smoking or alcohol consumption between men and women. Smokers had increased arterial stiffness compared to non-smokers. The number of cigarettes smoked over a lifetime was positively associated with increase in PWV. The authors noted that stopping smoking at young age can restore vascular health. Subjects who smoked at the age from 13 to 17 years, but subsequently stopped smoking, showed PWV comparable with non-smokers. In addition, no interaction between gender and smoking exposure in terms of its effect on vascular profile was found [42].

Alcohol

The relationship between alcohol consumption and peripheral arterial stiffness is not well studied. M. Charakida and collaborators (2019) found no positive effect of alcohol consumption on arterial stiffness even at lower levels of consumption. In addition, the study noted that it was the intensity of alcohol consumption, rather than the frequency of alcohol consumption and the type of alcoholic beverages, that was characterized by the greatest adverse association with arterial stiffness [42].

Data from Finnish study demonstrated direct adverse effect of consumption of small doses of alcohol on the thickness of the intima-media complex of the carotid arteries in young people [43].

C. L. Hwang and collaborators (2020) investigated the effect of regular binge drinking and moderate alcohol consumption on vascular stiffness in young men without CVD. The findings also suggest that regular exposure to alcohol, regardless of the type of

beverages, may increase arterial stiffness in healthy young people [44].

Sleep

In recent years, researchers have increasingly focused on the association of impaired sleep duration and quality with increased risk of CVD and target organ damage. One of the possible mechanisms of this negative effect are abnormalities of melatonin secretion, which has a number of endothelial-protective properties: melatonin increases the bioavailability of NO, activates antioxidant protective enzymes, binds free radicals, normalises lipid metabolism and BP. C. Agabiti-Rosei and collaborators (2017) studied the effect of melatonin on the anticontractile activity of perivascular adipose tissue and the expression of markers of inflammation/ oxidative stress in mouse aortic tissues. It turned out that long-term treatment with melatonin in mice with accelerated vascular aging increased expression of some markers of vasoprotective, reduced oxidative stress and inflammation and restored anticontractile effect of perivascular adipose tissue [45].

F.Y. Lee and collaborators (2018) in their study on mice which were given melatonin supplements for a long period of time, noted its protective effect on the structural and functional integrity of the vascular endothelium from oxidative stress, aging, critical ischemia due to the activation of SIRT (signal transduction pathway) [46].

The association of obstructive sleep apnea syndrome (OSA) with carotid artery remodeling in men without significant comorbidities should also be mentioned. When studying this topic, Grishchenko O. O. and collaborators came to the conclusion that sleep-related breathing disorders are associated with morphofunctional changes in the carotid arteries. They indicate structural rearrangement of the walls of the common carotid arteries, the formation of remodeling along mixed concentric-eccentric type, decrease in elasticity and increase in the stiffness of the wall of the common carotid artery. These features of carotid artery remodeling in patients with sleep-related breathing disorders were also associated with increase in vascular age by 12.5 % of the chronological age [47]. M. Çörtük and collaborators (2016) in their study of patients with OSA with a low and high apnea-hypopnea index found that the values of PWV were higher and the values of aortic extensibility were lower in the group of patients with a high apnea-hypopnea index [48].

Environmental factors

Air pollution

There is currently a lot of evidence that environmental pollution increases mortality and morbidity from CVD. According to the research back in 2015, environmental pollution contributed to 4.2 million deaths and was ranked as the 5th most important risk factor for mortality worldwide [49]. The exact mechanisms of the relationship between air pollution and increased cardiovascular morbidity and mortality are still unknown.

M. Lundbäck and collaborators (2009) reported that arterial stiffness increased immediately after 1 hour of exposure to diesel engine exhaust, while was no effect on arterial stiffness after 40 minutes of exposure [50]. It is likely that acute exposure to pollutants is associated with reversible increase in arterial stiffness. There may be several mechanisms involved in increasing the stiffness of large arteries after exposure to polluted air. In this regard, acute and chronic inflammation may play an important role in this process. Although only one of the studies included in this review examined the relationship between air pollution and biomarkers of vascular inflammation [51], the negative impact of air pollution on the development of inflammation is well known and widely documented in the literature.

Reversible increase in arterial stiffness may be a consequence of the development of endothelial dysfunction, due to a decrease in the amount of nitric oxide and a decrease in vasodilation. Irreversible increase in arterial stiffness may be associated with the production of uncoiled collagen, degradation of elastin, migration of smooth muscle cells and intima proliferation, vascular calcification and increased stiffness of the extracellular matrix. Increased arterial stiffness after short-term exposure to air pollutants is consistent with the conclusion that acute exposure to an inflammatory stimulus is associated with increased arterial stiffness and causes a reversible increase in arterial stiffness. In support of this hypothesis, there is evidence that exposure to particulate pollutants is associated with acute arterial vasoconstriction and endothelial dysfunction [52].

The Lancet published results of the study of the effects of road transport air pollution in participants over the age of 60 years. Participants were divided into 2 groups: one group walked for two hours a day along a busy commercial street in London (Oxford street), the second group walked daily around the London Park (Hyde Park). Participants in the second group showed improvement in lung function and

vascular condition within 24 hours after walking. Conversely, the condition of the blood vessels worsened after walking along Oxford street. Thus, even the positive effect of moderate physical activity on the cardiovascular system is leveled by inhaling polluted air [53].

Environmental noise

WHO estimates that at least 1 million years of healthy life are lost every year in high-income Western European countries due to environmental noise [54]. Negative health effects of noise include irritability, sleep disorders, and CVD.

Nighttime noise exposure appears to be more important for the occurrence of CVD, probably due to repeated vegetative excitations [55].

In a group of young and healthy volunteers, F. P. Schmidt and collaborators (2013) identified signs of significant endothelial dysfunction after just one night of exposure to aircraft noise. These changes improved markedly after vitamin C use, which may indirectly indicate a significant contribution of oxidative stress to this phenomenon. Endothelial dysfunction was accompanied by a significant increase in the level of circulating epinephrine and a significant dose-dependent decrease in sleep quality and increased SBP. It is likely that hypertension observed in response to nocturnal noise exposure can be explained by both increased sympathetic nervous system activation and the occurrence of vascular dysfunction [56].

In recent study M. Rojek and collaborators (2019) found that long-term (more than 35 years) exposure to aircraft noise (more than 60 dB) did not increase the frequency of hypertension, but was associated with higher office and night-time blood pressure levels and significantly higher PWV rates. These differences were independent of age, gender, BMI, education, time spent at home, smoking status, alcohol consumption, and antihypertensive therapy. The PWV of normotensive participants who were exposed to noise corresponded to that of normotensive older persons (20 years older) who were not exposed to noise [57].

Inflammation

Vascular wall inflammation is involved in vascular remodeling, thereby contributing to accelerated vascular wall damage in aging and hypertension, as well as in the initiation and progression of atherosclerosis and the development of cardiovascular and cerebrovascular diseases. In the early 2000s, the term "inflamm-ageing" was introduced, referring to chronic, sterile, low-intensity inflammation in the elderly. This concept denotes a wide range of immune disorders in the elderly, in which an increased level of pro-inflammatory factors persists with a simultaneous reduced immune response to immunogenic stimuli [58].

In the context of inflammation, an important role is played by adhesion molecules-vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), which increase on the membrane of endothelial cells at an early stage of the inflammatory process. This leads to the accumulation of monocytes/macrophages and lymphocytes in the arterial wall. Perivascular fat is also involved in vascular remodelling: it demonstrates inflammatory changes characterized by increased formation of inflammatory mediators, such as tumor necrosis factor alpha (TNF-α), and increased oxidative stress, as well as a decrease in adiponectin production [59].

Innate immunity may also be involved in vascular remodeling mechanisms by an imbalance between pro-inflammatory and anti-inflammatory T-regulatory lymphocytes [60].

In recent years, an interest in the state of the vascular wall of patients with inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC) has increased. Disorders above are characterized by both chronic systemic inflammation and episodes of acute inflammation during relapses of the disease. Although patients with IBD appear to have a low frequency of major cardiovascular risk factors, including obesity, dyslipidemia, and hypertension, the observed risk of coronary heart disease is high [61]. Previously researchers have suggested that this apparent contradiction, referred to as the "paradox of inflammatory bowel disease" may be at least partially explained by chronic inflammation and subsequent increased arterial stiffness [62].

Luca Zanoli and collaborators (2017) noted in their paper that aortic stiffness, measured by PWV, was increased in patients with UC and in patients with CD and depended on the duration of the disease and the number of white blood cells, but not on major risk factors for CVD and therapy [63]. It is likely that inflammation plays a key role in increasing aortic stiffness in patients with IBD. Another important finding of this study was that chronic inflammation increased aortic stiffness at any age. This suggests that the increase in arterial stiffness provided by

IBD may be a complement to normal aging. In addition, researchers did not find any connection between PWV and the level of C-reactive protein and the rate of erythrocyte sedimentation [64]. These results were confirmed even in subgroups, analysed separately in patients with UC and in individuals with CD. It is possible that measuring markers of active inflammation alone may not be sufficient to provide information about the relationship of chronic inflammation over time, since IBD is characterized by a wave-like flow. However, longitudinal studies are needed to confirm this hypothesis.

Psoriasis is a clinical model for investigating the effect of anti-inflammatory treatment on myocardial and vascular function. Increased production of interleukin 12 (IL-12), interleukin 6 (IL-6), TNF-α and oxidative stress contribute to the development of psoriatic lesions, which can lead to myocardial and vascular dysfunction [65].

In a randomized study, I. Ikonomidis and collaborators (2017) compared the effects of 4-month treatment with anti-IL-12/23 agents, anti-TNF-α, or cyclosporine on left ventricular myocardial deformity, coronary microcirculation, and arterial elasticity [66]. In psoriasis, increased IL-12 activity plays a key role in impaired arterial elasticity, coronary flow reserve, and myocardial deformation. Inhibition of IL-12 leads to a greater improvement in coronary flow reserve, arterial function, and myocardial function than inhibition of TNF-α or treatment with cyclosporine.

It is well known that patients with rheumatological diseases (RD) are characterized by a significantly higher level of cardiovascular morbidity and mortality compared to the general population [67]. The results of a study by A. L. Maslyansky and collaborators (2014) showed that the earliest and most characteristic manifestation of subclinical target organ damage in patients with autoimmune diseases is vascular wall remodelling, which results in increase in the thickness of the intima-media complex of the carotid arteries, and this may lead to accelerated progression of the atherosclerotic process and may be due to the combined influence of major CVD risk factors, inflammatory mediators, and disease-specific factors on the vascular wall [68].

It is notable to assess the relationship between target organ damage and the level of asymmetric dimethylarginine (ADMA), which is the most significant indicator of the state of endothelial function (an early predictor of the development of the atherosclerotic process) in various RD. Relationship between the serum concentration of a number of inflammatory mediators (mip-1b, il-6, ifny, C-reactive protein) and ADMA was detected. In experimental and clinical conditions, ADMA levels were shown to increase against the background of immune activation/current inflammatory process. Researchers have previously identified independent and significant effects of chemokines and cytokines: mip-1b, il-6, and C-reactive protein on ADMA levels [69]. On the other hand, ADMA has the properties of an inflammatory mediator, stimulating the adhesion of lymphocytes and the production of chemokines. ADMA is also characterized by a wide range of vasotoxic effects, which include inhibition of NO-synthetase, the ability to change the phenotype of endothelial cells (accelerated aging), cause platelet dysfunction, and increase the proliferation of smooth muscle cells in the media. This allows us to consider ADMA not just as a marker, but also as a mediator of endothelial dysfunction and vascular wall remodelling. The possibility of using ADMA level as an early marker of the atherosclerotic process was demonstrated in one of the studies of 202 healthy individuals aged 45–70 years. In 80 of them subclinical carotid atherosclerosis and a higher ADMA level were detected, which correlated with the thickness of the intima-media complex [70].

Oxidative stress, usually considered a major factor in biological aging, is amplified in end-stage renal disease (ESRD) and is related to uremic inflammation [71]. J. P. Kooman and collaborators (2017) in a recent study studied possible causes of uremic inflammation [72]. It is likely that elevated serum phosphate levels can lead to cellular and physiological aging. A surprising result was observed in a study on uremic rats, in which the process of calcification of dietary phosphate was actually enhanced by a diet with a very low protein content and was also associated with an increase in TNF levels and a decrease in fetuin levels [73]. Fetuin mediates the formation of calciprotein particles, circulating colloidal complexes containing calcium and phosphate, which are catabolized by the mononuclear phagocytic system [74]. However, the formation of calciprotein particles also leads to a decrease in circulating and intracellular fetuin levels, with a potential loss of protection from extracellular calcification.

Conclusion

The main goal of preventive cardiology is to find the most effective ways to prevent CVD and

mortality. Some prevention methods are well known and have an impressive body of evidence (increased physical activity, healthy nutrition, normalization of sleep, quitting of smoking and limitation of alcohol consumption), other factors for maintaining "ideal arteries" have yet to be thoroughly studied and put into practice (telomere length, epigenetic factors, intestinal microbiota). Determining the biological age should become a routine procedure for a more accurate assessment of the patient's therapeutic status and treatment tactics, especially in young patients with infavorable heredity and low adherence to medical recommendations. Determining vascular age can be both a step in assessing cardiovascular risk and a powerful argument for a patient to change their lifestyle and initiate therapy.

It is worth noting that arterial stiffness reflects not only current vascular damage, but also its regression with effective therapeutic intervention and progress with continued exposure. The establishment of opposite sides, such as EVA and SUPERNOVA, is the result of an interaction between structural changes in the vascular wall (most often associated with age) and processes that accelerate/slow this progress. The approach of identification of patients with EVA and SUPERNOVA, studying epidemiology and predictors of those syndromes will help to identify protective cardiometabolic, genetic and epigenetic factors that can be used to develop new treatments. Efforts are needed both to optimize the achievement of target levels when taking antihypertensive, hypoglycemic, and hypolipidemic therapy, and to search for yet unknown factors that cause residual risk.

Conflict of interest / Конфликт интересов

The authors declare no conflict of interest. / Авторы заявили об отсутствии конфликта интересов.

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