VASCULAR AGING: PATHOPHYSIOLOGICAL MECHANISMS, CLINICAL IMPLICATIONS, AND PREVENTIVE STRATEGIES

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Abstract

Vascular aging carries a major function in mortality and morbidity among the elderly due to the increased frequency of cardiovascular events. To develop novel preventive and treatment strategies for early vascular aging, it is crucial to know the pathophysiological changes in the blood vessels during the aging process. In this review, we present the molecular mechanisms of vascular aging, including mitochondrial dysfunction, activation of inflammation, epigenetic alterations, and genomic instability. The importance of various diagnostic methods of vascular aging determination and clinical manifestations are discussed. Finally, current preventive strategies to postpone alterations associated with the aging process in the vasculature by targeting the pathophysiological mechanism of aging are presented.

Keywords: vascular aging; blood vessels; cardiovascular diseases; risk factors; prevention.


Introduction

Cardiovascular disease (CVD) belongs to the leading cause of death and increased by 60% globally over 30 years [1]. Due to the gradual aging of populations and increased frequency of CVD at younger ages, vascular aging, and premature aging are crucial topics of research.

Vascular aging (VA) is continuous changes of the medial layer of the large artery wall (usually asymptomatic), consisting of a progressive reduction in elastin levels and an elevated amount of collagen, that causes increased arterial stiffness [2]. Early vascular aging (EVA) definition includes premature damage in artery structure and function compared to matched age and sex [3]. It is widely recognized that older age significantly contributes to the risk of CVD. However, its direct effects on the blood vessels are not clear. Generally, age is going together with other cardiovascular risk factors. Enhanced comprehension of these irreversible vascular mechanisms could help to provide a clinical strategy for the management of individuals at an increased risk for CVD and to improve longevity.

This study aims to highlight some molecular mechanisms in vascular aging, a possible role of oxidative stress, genetic factors, vascular inflammation, extracellular matrix metalloproteinases activity, its clinical associations, and prevention of early vascular aging.
Search strategy

We searched MEDLINE/PubMed and Scopus until June 2023 following previously published recommendations [4]. The following Medical Subject Heading (MeSH) keywords were used: “Blood Vessels”, “Vascular”, “Aging” in combination with “etiology”, and “prevention and control”. We processed reviewed and original articles including case reports. Conference abstracts, book chapters, and preprints were excluded.

Molecular mechanisms and physiology of VA

The molecular mechanisms underlying the process of aging in all types of blood vessels are closely linked to cellular alterations that impact the morphology and physiological capabilities in tissues, which comprise the blood vessel (Figure 1). Mitochondrial dysfunction is a critical mechanism that emerges as a result of the accumulation of damage to mitochondrial DNA and a reduction in the activity of the respiratory chain’s enzymes. Consequently, a decrease in energy generation and the buildup of unpaired electrons, known as free radicals, occur, resulting in the occurrence of oxidative stress. The notion that mitochondria are involved in chronic heart failure through reactive oxygen species (ROS) is supported by the observation that senescent cells without mitochondria show significantly lower levels of mitochondrially produced ROS compared with senescent cells treated with an inhibitor of mitochondrial oxidative phosphorylation [6]. The aging process is characterized by the formation of cytoplasmic chromatin and inflammation, which is driven by retrograde signaling from mitochondria to the nucleus.

Oxidative stress arises from a state of disequilibrium between the free radical’s production and the antioxidant’s protective mechanisms. The presence of free radicals has been shown to cause damage to various parts of the cells such as DNA, proteins, and lipids.

Figure 1. The main pathophysiological mechanisms and clinical consequences of vascular aging.
This damage can result in the initiation of the inflammatory cascade with a synthesis of pro-inflammatory cytokines and chemokines. There is a correlation between the reduction in the availability of nitric oxide (NO) in the endothelium and the elevation in ROS production [6]. Tetrahydrobiopterin (BH4), which is also referred to as BH4, plays a vital role as a cofactor for nitric oxide synthase (NOS) [7]. Decreased availability of BH4 causes dissociation of endothelial NOS and subsequent increase in ROS production. The administration of liposomal BH4 in the post-ischemic heart has been found to maintain the coupling of endothelial NOS, thereby providing in vivo cardioprotection [8].

Under oxidative conditions, the compound BH4 undergoes oxidation, resulting in the formation of bipterin and dihydrobiopterin. The last one competes with the BH4 for the NOS binding site, resulting in a further reduction in NOS-catalyzed nitric oxide production [9]. During the phenomenon known as endothelial NOS-uncoupling, the consistent transfer of electrons from the reductase to the oxygenase domain, which facilitates the transformation of L-arginine into vasoprotective NO, is interrupted. In contrast, the redirection of electrons towards oxygen results in an increase in the synthesis of inline images and a reduction in the generation of NO by endothelial NOS. Senescent endothelial cells demonstrate an increase in the expression and activity of Arginase-II. However, the suppression of Arginase -II in these cells results in a significant reduction in endothelial NOS-uncoupling and the expression of markers of senescence, like p53-S15 and the activity of senescence-associated β-galactosidase, VCAM1 and ICAM1 [10]. The process of eNOS-uncoupling facilitates Arginase-I in promoting endothelial inflammation and aging [11].

The process of blood vessel aging is characterized by increased activation of inflammatory mechanisms [12]. This phenomenon is correlated with an augmentation in the synthesis of inflammatory cytokines (such as tumor necrosis factor-α (TNFα) and interleukin (IL)-6 and IL-1β), chemotactic proteins, and molecules involved in cellular adhesion [13]. Inflammation promotes the entry of immune cells into the bloodstream, triggers fibrosis activation, induces both morphological and functional damages in the vessel walls, and stimulations of immune cells, specifically macrophages, and monocytes.

The dysfunction of endothelial cells initiates the vascular low-grade inflammatory processes. In instances of inflammation, there is a notable elevated production of ROS and reactive nitrogen species (RNOS), which presents a potential hazard for DNA integrity. The occurrence of elevated levels of ROS generation in the intracellular or tumor microenvironment is correlated with a diminished ability to regulate cellular proliferation [14].

There is a correlation between blood vessel aging and both telomerase activity and shortening of telomeres [15]. Telomeres undergo gradual shortening due to the effects of aging and cellular replication. Once telomeres reach a critically short length, they cause cellular senescence mechanisms, resulting in the cessation of cell proliferation and a decline in the ability of vascular tissues to regenerate. A change in the structure of telomeres can result in genomic instability and DNA damage. This can further exacerbate cellular senescence and ultimately lead to organ degeneration. Telomere length undergoes reduction during each instance of cell division because of the incapacity of a specific reverse transcriptase enzyme (telomerase) to replicate the sequences situated at the terminal end. This process is reliant on the non-coding RNA template TERC [16]. Controlling the expression and maintenance of telomerase, as well as aging markers, is governed by AUF1, an endogenous factor, through two separate mechanisms that are interrelated with the inflammatory response. The AUF1 protein is critical in maintaining the normal aging process, preserving telomere length, and preventing cell senescence through its ability to activate telomerase transcription [17].

Tissue aging in the circulatory system encompasses alterations in histone modifications and DNA methylation at the epigenetic level [18]. These alterations have the potential to exert an influence on the activity and regulation of genes, thereby affecting the functional attributes of blood vessels. Chromatin functions as the fundamental architectural frame for the arrangement of the complete genome. Constitutive heterochromatin, which is situated in pericentromeric and telomeric regions, exhibits the presence of histone-3 lysine-9 tri-methylation (H3K9me3) [19]. Furthermore, H3K9me2 has been identified as a possible indicator of inactive euchromatin. The process of aging is associated with a decrease or rearrangement of H3K9me3/2, which leads to the structural reorganization of heterochromatin. This phenomenon leads to a reduction in the repression of constitutive heterochromatin loci and a concomitant escalation in facultative heterochromatin in other sites of the genome. In regions of facultative heterochromatin, the presence of H3K27me3 can be observed, and its repression exhibits greater specificity towards particular cell types. H3K27me3 experiences dynamic modifications to facilitate the repression or de-repression of gene clusters during the processes of development or differentiation [20].
The mRNA expression is influenced by the presence of essential and controlling splicing elements, with certain factors being subject to regulation through the involvement of the DNA damage response protein ATM. The data presented in this study hold great importance as they have the potential to reveal a fundamental association between DNA damage that occurs with age and the complex mechanisms of alternative splicing. These mechanisms are known to influence adaptability, plasticity, and cellular identity. The expression of splicing factors is observed to undergo alterations in correlation with the progression of age in human individuals [21].

Diagnostic methods of VA determination

As vascular-aging markers, a series of molecules linked to the pathology process mentioned above are available. However, there are no currently available studies to validate these blood vessel biomarkers [22]. Moreover, the methodology for the clinical use of these markers has not been agreed upon. None of them is compliant with all the clinical application criteria [23].

Therefore, the non-invasive methods of diagnosis related to VA that can predict clinical CVD will become a key issue in this section based on data and recent research. The pulse wave velocity (PWV) stands as the most important type of VA diagnosis. It is a characteristic of arterial stiffness that is calculated by the formula $PWV = \frac{\Delta L}{\Delta T}$, where $\Delta L$ is the distance between 2 measuring points, and $\Delta T$ is the time it takes for the arterial pulse to travel from the proximal to the distal measuring site [24]. This test is fast, with a duration ranging from 5 minutes to 20 minutes, non-invasive, and does not require difficult preparation. PWV in clinical practice can be measured in different body parts - the most common is between carotid and femoral arteries on the same side, or brachial and ankle on the same side. The cardio-ankle vascular index is also popular, but in this case, the usage of Doppler ultrasound for measuring the flow wave has been suggested as a better and more accurate way comparing using pressure cuffs [25]. Oscillometric, tonometric, volume plethysmographic, and photo-plethysmographic devices can evaluate PWV [26].

The next commonly used type to measure PWV is by using Doppler ultrasound for the assessment of superficial arteries (carotid artery), and magnetic resonance imaging (MRI) for a focused assessment of central arterial stiffness (the aortic arch). MRI angiography can measure the cross-sectional diameter of the vessels. 2D or 3D MRI is showing how an artery or vein passes through anatomical structures, it allows us to see the form of the vessel and allows us to see changes that occur over the years (for example, wall thickness, homogeneity, change in lumen radius) [27]. However, it should be noted that early stages of some vascular pathologies like atherosclerosis can’t be seen in angiography, and this can be explained by Glagov’s phenomenon: when atherosclerotic plaque starts to develop it grows outwardly, and these changes are impossible to see on angiographic images, but arterial stiffness can be measured. Only in the terminal stages when plaque blocks the lumen of the vessel, it can be seen in computer tomography or MRI angiography [28].

Photoplethysmography (PPG) is an optical technique that records the rhythmic alteration in blood volume within blood vessels with every heartbeat. PPG-based instruments find applications in various scenarios, including clinical settings like pulse oximetry [29], as well as in daily life through devices such as smartwatches and fitness bracelets that record continuous or intermittent measurements which can be worn on a variety of parts of the body, like fingers, wrists and ears. In terms of their convenience and availability, the methods for PPG assessment in blood vessel aging are efficient and potentially clinically useful [30]. The correlation between certainly derived indices and both the carotid-to-femoral PWV and the presence of peripheral arterial disease has been detected [31]. For the measurement of aortofemoral volume wave velocity, segmental plethysmography uses special electrodes positioned on standard ECG leads, positioned on the right side of the neck, enabling the creation of arterial impedance plethysmograms for all four limbs. The correlation between cardiovascular risk factors and the onset of arterial hypertension in young individuals has been established [32]. The measurement of PWV for the finger toe is carried out with the careful placement of photoplethysmography sensors on the pulpar artery, both toes and fingers. A publication demonstrating significant improvements and validations in the adult population was made available, showing exemplary alignment between reference methods and detection algorithms [33]. A method was proposed in 2022 to assess VA using deep learning of PPG, identifying the shape of PPG’s original waveform that contributes to assessing VA through artificial intelligence [31].

The suggested deep learning approach for estimating vascular aging demonstrates similarity to the existing feature-based analysis and exhibits superior performance. However, it has not yet been used to detect features. According to the data expansion, deep learning techniques should be able to perform a more accurate assessment of aging in vessels compared with empirical and manually determined features. It is not just the potential for evaluating VA through PPG evaluation that
this study proposes but also gives an insight into fundamental scientific principles and reasoning behind their assessment of VA by interpretation of results using explainable artificial intelligence. These factors are vital to the discovery of vascular aging’s distinctive characteristics, such as those observed in PPG.

VA: clinical consequences

The structural changes due to VA are mostly localized in the middle lamina of large elastic arteries and are characterized by increasing arterial stiffness and expanding vascular wall thickness. It is difficult to determine the contribution of various risk factors from the traditional cardiovascular continuum (Dzau, 2006) to the development of cardiovascular events [34]. Therefore, arterial stiffness reflects an early and cumulative effect, indicating actual damage to the arterial wall [35]. This results in elevated systolic blood pressure and reduced fluctuations in diastolic blood pressure [36]. The «cardiovascular continuum» by Dzau et al. informs about the CVD progression [34], based on the process of atherosclerosis, which emerges as a result of the effects of conventional cardiovascular risk factors, progressing through the stages ending with coronary artery obstruction, ischemia, myocardial infarction, heart failure, and death. Also, the main thing is the progressive structural changes of the aorta with a harmful effect on the target organs. As a result of obstructive and ischemic disease of the arteries, an increase in PWV is manifested. An elevation of 1 m/s in aortic PWV is linked to a 15% rise in CVD and all-cause mortality [37].

Hypertension is a recognized factor contributing to the risk of cerebrovascular disorders like microangiopathy and white matter lesions more prevalent among older individuals. Cognitive dysfunction and a heightened likelihood of dementia is the main outcome in these patients and occur several years earlier in people with a combination of EVA and hypertension [38].

The progression of atherosclerosis within cerebral blood vessels leads to hypoperfusion with detrimental neurological consequences. Cerebrovascular atherosclerosis has been shown a cornerstone sign of Alzheimer’s disease (AD). Roher et al. identified that AD patients compared to the age-matched controls have significant severe atherosclerosis within the arteries of the circle of Willis [39]. The other study demonstrated that atherosclerosis of cerebral blood vessels is linked to decreased cognitive measures and an elevated risk of AD [40]. The connection between atherosclerosis and the development of AD extends beyond just intracranial vessels to include extracranial arteries as well. The occurrence of AD triples in patients with severe atherosclerosis in the carotid and femoral arteries, especially in carriers of apolipoprotein E4 (ApoE4), which represents the primary genetic susceptibility element for the onset of AD [41]. The underlying pathological mechanisms connecting atherosclerosis and AD may encompass chronic inflammation, compromised clearance of amyloid beta (Aβ), and the vascular effects of ApoE4 [42].

In contrast, patients may exhibit unusually reduced arterial stiffness considering their age and gender, a phenomenon termed the supernormal vascular aging (SUPERNOVA) phenotype, which has been newly recognized. This concept also includes individuals who still have elastic arteries and normal blood pressure even in the presence of exposure to cardiovascular risk factors. Epidemiological studies revealed that even individuals within high-risk categories (long-term type 1 diabetes) with exposure to the Western lifestyle can manage to evade significant cardiovascular incidents, irrespective of their glycemic management [43].

Prevention of premature vascular aging

To slow down the aging of blood vessels, it is necessary to carry out their prevention.

Regular physical exercises

The different types of exercises resulted in consistent improvements in endothelium-dependent vasodilation [44]. These findings support the hypothesis that resistance training (RT), cardiovascular training (CT), and aerobic training (AT) can all lead to similar enhancements in endothelial function. Notably, these improvements were achieved with moderate exercises performed twice a week over a relatively short duration of 8 weeks. Also, AT and RT were found to reduce 24-hour systolic BP, whereas CT did not have the same effect. Only two randomized controlled trials have investigated the persistent impact of various exercise modalities on endothelial function in individuals diagnosed with arterial hypertension [45]. These studies provide valuable clinical insights into combating endothelial dysfunction as a significant cardiovascular risk factor among patients about 40 years with prehypertension or arterial hypertension.

The physiological mechanisms underlying the improvement in endothelial function through regular exercise can be explained by the repeated perfusion that results in increased shear stress on the vascular wall. This explanation is particularly applicable to aerobic exercise.
On the other hand, the pathogenesis by which strength training contributes to the improvement of endothelial function is not fully studied. It is postulated that the mechanical compression exerted on skeletal muscles during strength-based exercises may induce excessive vascular stress, potentially leading to endothelial damage. However, studies have reported an increase in reactive forearm hyperemia after half a year of strength training in healthy young adults. During strength training, the compression of supporting vessels caused by muscle contractions results in transient ischemia. Subsequent relaxation of the muscles leads to blood flow release, causing hyperemia and an increase in shear stress. Both aerobic exercise and strength training provide similar benefits to endothelial function.

Numerous international medical organizations recommend regular exercise as an initial lifestyle intervention for patients with arterial hypertension. Results from a meta-analysis demonstrated that twice-weekly moderate-intensity exercise for 8 weeks decreases blood pressure among individuals with prehypertension or arterial hypertension [46]. These decreases in blood pressure have the potential to lower the risk of stroke by 14%, coronary heart disease by 9%, and overall mortality by 7%. Moreover, the reductions in blood pressure achieved through exercise training are comparable to those achieved with first-line antihypertensive medications.

**Dietary preferences**

Additionally, selecting a diet with proven cardiovascular protective effects is beneficial. One such diet is the ketogenic diet. It was shown that ketogenic diets can regulate miRNA expression, which in turn regulates antioxidant and inflammatory status in obese patients [47]. These diets also improve inflammatory conditions by reducing weight, influencing the gut microbiota, decreasing insulin resistance, and improving lipid profile.

The Dietary Inflammation Index (DII) evaluates the inflammatory potential of different 45 micro- and macronutrients. Diets that are low in advanced glycation products (AGEs) have proven effective in both preventing and ameliorating metabolic inflammation. Such diets have been associated with decreased levels of TNFα, VCAM1, and leptin, while concurrently elevating sirtuin-1 and adiponectin levels [48].

The Mediterranean Diet (MedDiet) is another diet that offers health benefits due to its antioxidant, anti-inflammatory, and anti-atherosclerotic effects [49]. Individuals following the MedDiet have lower levels of inflammatory markers and reduced cardiovascular risk factors. Additionally, the MedDiet may play a role in anti-aging as it is positively linked to the length of telomeres [50].

Findings from the EVA study suggest that a more robust commitment to the MedDiet is associated with a reduced likelihood of experiencing early vascular aging. Nevertheless, this association appears to be specific to men when analyzed by sex [51].

**Pharmacological prevention**

Various treatments can exert beneficial effects on vascular aging, including vitamin D, statins, anti-inflammatory and antidiabetic drugs. The influence of vitamin D supplementation on endothelial dysfunction has been evaluated in numerous clinical trials among patients with various chronic vascular diseases [52]. The efficacy of vitamin D in endothelial function improvement was associated with the duration of treatment, the dosage of vitamin D, and the underlying conditions.

Statins, the drugs that target dyslipidemia, are effective in atherosclerosis stabilization and regression. They have shown efficacy in arterial stiffness reduction due to decreased PWV in patients with systolic hypertension, obesity, and hypercholesterolemia [53, 54]. In addition, the statins reduced the increase in carotid IMT during 10 years of observation [55]. The main efficacy is achieved by regulation of visfatin, adiponectin, and leptin levels, leading to reduced inflammation as indicated by decreased CRP levels.

Antidiabetic drugs: insulin and novel oral glucose-lowering drugs also have anti-inflammatory effects due to the reduction of inflammatory markers levels.

Immunobiological agents, such as inhibitors of IL-1 (canakinumab and anakinra), have demonstrated a reduction in the risk of major cardiovascular events in patients with a previous myocardial infarction, CRP levels and improved exercise tolerance in patients with heart failure [56, 57]. Colchicine plays a role in suppressing the NLPR3 inflammasome, thereby reducing the production of IL1 and CRP. According to the data from the COLCOT, COPS, LoDoCo, and LoDoCo2 trials administration of 0.5 mg/day of colchicine resulted in a significant reduction (32%) in cardiovascular death, myocardial infarction, stroke, and emergency revascularization compared to placebo [58-61]. 2021 ESC guidelines on the prevention of CVD have recommended considering colchicine for the secondary prevention of CVD, in particular for those with uncontrolled risk factors.
and recurrent cardiac events despite optimal medical therapy [62].

Conclusion

In recent years, a variety of molecular markers of vascular aging have been discovered. The understanding of the pathogenesis of vasculature changes is a basis for preventing or treating vascular pathologies associated with aging. In conclusion, timely diagnosis of early vascular aging and active implementation of preventive measures will contribute to the reduction of morbidity and mortality from cardiovascular diseases.

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