

Progress of clinical evaluation for vascular aging in humans

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ABSTRACT

Human society is experiencing a serious aging process. Age-related arteriosclerotic cardiovascular diseases (ASCVD) are the most common cause of deaths around the world and bring a huge burden on the whole society. Vascular aging-related pathological alterations of the vasculature play an important role in the pathogenesis of ASCVD and morbidity and mortality of older adults. In this review, we describe the progress of clinical evaluation of vascular aging in humans, including functional evaluation, structural assessment, and cellular molecular markers. The significance of detection for vascular aging is highlighted, and we call for close attention to the evaluation for a better quality of life in the elderly population.

Key words: vascular aging, clinical evaluation, arteriosclerotic cardiovascular diseases

INTRODUCTION

The famous 17th-century physician Thomas Sydenham, recognized as “English Hippocrates” and the author of *Observationes Medicae*, observed, “a man is as old as his arteries”. Indeed, the world is stepping into an aging society. Aging is a major risk factor for the occurrence of arteriosclerotic cardiovascular diseases (ASCVD), which are the leading causes of long-term disability and mortality among the elderly around the world.^[1] Importantly, advanced aging is the single most essential risk factor that dwarfs the effect conventional risk factors (*e.g.*, hypertension, hyperglycemia, hypercholesterolemia),^[1] and age-related ASCVD account for nearly half of all deaths worldwide (World Health Organization), consequently, addressing the value of clinical evaluation of age-related vascular diseases is considerably meaningful. Vascular aging causes multifaceted structural and functional vessels’ impairment, which shows the deleterious impact on cellular metabolism and function, and thus leads to the pathogenesis of ASCVD.^[2] Thus, for better

amelioration of unsuccessful vascular aging and prevention of age-related vascular pathologies, it is critical to identify vascular aging and dysfunction from multiple perspectives as to prevent the occurrence and development of vascular disease associated with old age (Table 1).

FUNCTIONAL EVALUATION OF VASCULAR AGING

Vascular endothelial dysfunction is the initial process of vascular aging-related ASCVD. Detection for vascular function is of great significance to identify the vascular risk and prevent the pathogenesis of vascular-related ASCVD. In recent years, with the continuous development of vascular function research and the update of technology, noninvasive function detection indicators reflecting vascular aging have gradually been used in clinical and scientific research. At present, a large number of studies have confirmed that early detection of flow-mediated dilation (FMD),^[3] brachial ankle pulse wave velocity (baPWV)^[4] and ankle brachial index (ABI)^[5] are important strategies to slow down vascular aging. In

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Table 1: Clinical evaluation for vascular aging in humans

Clinical evaluation	Methods	Description
Functional evaluation	FMD	FMD, carried out noninvasively with ultrasonography on the brachial artery, is a commonly used method for the evaluation of endothelial dysfunction. FMD provides a non-invasive, cheap, and repeatable measure of endothelial function and has been widely used in pathophysiological studies and management of aging vessels.
	baPWV	baPWV has been reported as an index of arterial stiffness and serves as an indicator of cardiovascular risk and the severity of vascular aging-related damage.
	Endo-Pat	Endo-PAT, a safe, accurate, and non-invasive diagnostic device, is used for evaluating both small and large arteries to detect the status of vascular function and earliest stages of cardiovascular diseases.
	Infrared thermal imaging technology	Infrared thermal imaging technology is a method to improve visibility of participants in a dark environment by detecting their infrared radiation, in order to reflect the microcirculation and reveal the vascular function.
Structural assessment	MRI	MRI is a non-invasive imaging method, which provides high spatial resolution for the morphological and compositional evaluation of the vessel wall and is a promising modality for assessment of vascular aging.
	IMT	Carotid intima-media thickness is a surrogate measure of aging associated with cardiovascular risk factors and with cardiovascular outcomes, for detection of early stages of atherosclerosis and evaluation of arterial wall structure.
	CTA	CTA is a vascular imaging technique that can be carried out rapidly and safely for the evaluation of aging-related artery disease as well as other vascular applications.
	OCTA	OCTA has emerged as a fast, safe, and noninvasive procedure to provide depth-resolved images of blood flow in the retina and assess the retinal microvasculature, which is essential for the early detection of age-related chronic diseases, especially diabetes and hypertension.
Cellular molecular markers	EPCs	EPCs are bone marrow-derived endothelial precursor cells and participate in the endothelial repair and endothelial function regulation, which is a surrogate biologic measure of vascular function and human age.
	EMPs	EMPs are microparticles that are detached from the cell membrane of endothelial cells. The increasing level of EMPs is associated with the prognosis of age-related diseases.
	Sirtuins	Sirtuins, a class of NAD ⁺ -dependent deacetylases, are implicated in numerous biological pathways and are considered as an index of aging and a promising target for treating human diseases.
	Telomere and telomerase	Telomeres and telomerase are important in maintaining the chromosomal stability and integrity. The length of the shortest telomere is a key biomarker of the onset of aging.
	Mitochondria and superoxide flashes	Superoxide flashes are brief bursts of superoxide production within the matrix of single mitochondria and exhibit all-or-none properties. It has emerged as a relatively early and pivotal event of cell metabolism, differentiation, the stress response, and aging.
	Nucleolus	Maintenance of nucleolar homeostasis is demonstrated to contribute to counteracting cells' aging because of the stability of DNA synthesis.
	cfDNA	cfDNA, all non-encapsulated DNA in the blood stream, can be recognized as a new biomarker of aging according to recent studies.
	Humanin	Humanin is an innovative 24-amino acid mitochondrial-derived peptide that has demonstrated cytoprotective effects. Humanin decreases with age in several species, including humans.
Ageotype	Ageotypes may provide a molecular assessment of aging and reflect lifestyle and medical history, in order for better intervening in the vascular aging process.	

FMD: flow-mediated dilation; baPWV: brachial ankle pulse wave velocity; MRI: magnetic resonance imaging; IMT: intima-media thickness; CTA: computed tomographic angiography; OCTA: optical coherence tomography angiography; EPCs: endothelial progenitor cells; EMPs: endothelial microparticles; cfDNA: cell-free DNA

addition, more and more new technologies have been applied to the detection of vascular function.^[6]

FMD and baPWV

FMD is the method describing the vascular vasodilation caused by the increase of lumen blood flow and shear stress. FMD decreased in patients with elevated blood pressure, and endothelial function assessed by FMD was impaired regardless of the blood pressure level of hypertensive

patients after antihypertensive drug treatment^[3]. At the same time, FMD is also an important assessment method of target organ injury.^[7]

baPWV is another main index to detect the degree of arteriosclerosis, and its change is the overall reflection of abnormal structure and function of arteries. The results showed that baPWV was an independent predictor of hypertension, and the risk ratio of baPWV increased by 1

m/s was 1.10.^[8] Based on the traditional cardiovascular risk factors, measuring baPWV can improve the effectiveness of predicting the development risk of ASCVD.^[9]

Endo-Pat

Endo-Pat is based on a set of plethysmography biosensor system, which is used to measure the endothelium vasodilation and contraction function after reactive hyperemia at fingertips, and the result is presented as reactive hyperemia index (RHI). The study found that the sensitivity and specificity of 1.67 as a critical value of RHI for the diagnosis of endothelial dysfunction were 82% and 77%, respectively.^[10] Endo-Pat is of great significance for screening of high-risk population and has gradually been set as a clinical function evaluation indicator of vascular aging.^[11, 12]

Infrared thermal imaging technology

Infrared thermography, based on the principle of remote temperature measurement, records the infrared radiation wavelength emitted by human skin (affected by skin vascular relaxation and contraction factors) to analyze the multiple information of body surface temperature, and displays it in the form of thermal map, so as to reflect the microcirculation, the blood circulation of the lesion site, *etc.*^[13] The study found that infrared thermal imaging technology has unique value in screening large population, detecting vascular function of chronic diseases such as hypertension, diabetes, and their complications.^[14-16]

STRUCTURAL ASSESSMENT OF VASCULAR AGING

The integrity of vascular structure is an important guarantee for the normal function of blood vessels, and it is also the key factor to maintain vascular health and delay vascular aging. At present, vascular structure evaluation indicators are gradually applied to clinical practice, including magnetic resonance imaging (MRI), carotid intima-media thickness (IMT), computed tomographic angiography (CTA), *etc.*

MRI

In the case of endothelial dysfunction and structural dysfunction, vascular hyperemia becomes blunted and can be measured noninvasively by a variety of quantitative MRI methods, including a blood oxygenation-level-dependent (BOLD) signal that reflects the combined effect of blood flow and capillary bed oxygen content, arterial spin labeling (ASL) for quantification of regional perfusion, phase contrast (PC) to quantify arterial flow waveforms, macrovascular blood flow velocity and rate, *etc.*^[17] In the development of vascular aging, BOLD MRI can also be

observed even in the absence of obvious ASCVD.^[18, 19] Some studies have also found that there is an association between ASL-based measurement and the occurrence and severity of peripheral vascular disease.^[20, 21] In addition, based on the baseline characteristics of PC and arterial blood flow waveform, endothelial structure and function, vascular reactivity and blood flow reserve can be deeply understood.^[22] MRI can also be used to quantify the cross-sectional area of blood vessels and to evaluate the structure of vascular wall or hemodynamics.^[23]

IMT

Carotid IMT refers to the distance between the lumen surface of carotid intima and the interface of adventitia. IMT increases linearly with age and is considered as an independent risk factor for cardiovascular events.^[24, 25] At present, the international reference values recommended according to different ages are as follows: 40–49 years, <0.7 mm; 50–59 years, <0.8 mm; and 60 years or older, <0.9 mm.^[26] Early identification and intervention of IMT plays an important role in delaying vascular aging and preventing subclinical development of atherosclerotic vascular disease.^[27]

CTA

As a common clinical technique, CTA exerts essential role in the diagnosis of vascular structure variation and diseases. Recent studies found many novel noninvasive technologies such as CT-derived fractional flow reserve (FFR) for estimating the blood flow distribution and predicting the functional outcome after coronary stenting.^[28, 29] Other research showed that CTA may identify coronary arterial abnormalities and add information on coronary artery lesions in patients with Takayasu arteritis (TA), which acknowledges CTA as a useful technique in figuring out the pathological changes in the vessels.^[30]

Optical coherence tomography angiography (OCTA)

Retinopathy caused by age-related diseases, especially diabetes mellitus and hypertension, is a serious neurovascular complication, which is a primary reason of blindness in the aging population.^[31] OCTA is a promising and emerging technique for imaging the retinal vasculature without dye injection, and it appears as a comprehensive management of retinopathy related to vascular aging.^[32] OCTA visualizes the ocular blood flow in the retinal network and is essential for locating and measuring the sizes of various pathological alternations. Studies have demonstrated that OCTA shows a favorable effect on detecting angiographic features, even before the disease onset, which may be a useful method for vascular aging-related diseases.^[33]

CELLULAR MOLECULAR MARKERS OF VASCULAR AGING

At present, there is a lack of a universal marker for the detection of vascular aging. As the molecules expressed by senescent cells will change with the different cell types, senescence stimulation, and stimulation time, the phenotype and molecular markers of cell senescence still need to be further studied.

Endothelial progenitor cells (EPCs) and endothelial microparticles (EMPs)

EPCs are bone marrow-derived endothelial precursor cells that are present in peripheral blood. They can be directed to the vascular injury site and differentiate into mature endothelial cells, which is recognized as a landmark of the capacity of vascular repair. Studies found that circulating EPCs deficiency contributes to reduced arterial elasticity in persons of advancing age,^[34] and impaired EPCs activity is associated with impaired vascular function.^[35,36] These results demonstrated that the decrease in circulating EPCs number and activity may serve as a surrogate biologic measure of vascular function and human age.

EMPs are microparticles that are detached from the cell membrane of endothelial cells during activation, metabolism, apoptosis, and other cellular process. Elevations of EMPs in the circulation, mostly defined as CD31+/CD42+ microparticles, as well as alterations in their phenotype, were found in various pathological conditions related to endothelial dysfunction.^[37] In addition, EMPs increase along with aging and vascular damage and emerged as the sensitive marker of endothelial perturbation in response to adverse stimuli.^[38] Therefore, increasing level of EMPs is associated with prognosis of ASCVD, suggesting vascular aging.

Sirtuins

Sirtuins are a class of NAD⁺-dependent deacetylases. Anti-aging properties of sirtuins were first observed in 1999, for its overexpression was demonstrated to increase yeast lifespan by 70%.^[39] Growing evidence has shown that sirtuins are essential for vascular aging through repair DNA damage, lowering oxidative stress, and alleviating inflammation.^[40] For instance, SIRT1 is one of the most extensively studied proteins because of its capability of delaying vascular aging and preventing age-related diseases by catalyzing protein deacetylation and regulation of a series of transcription factors and coactivators, such as the forkhead box O (FOXO), nuclear factor-kappa B (NF- κ B), and peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1 α).^[41] Besides, SIRT3 and SIRT5, two major NAD⁺-dependent deacetylases located

in mitochondria that deacetylases mitochondrial proteins at their lysine residues, are confirmed to be beneficial for improving vascular functions via maintaining the balance of oxidative stress and augmenting the capacity of angiogenesis.^[42, 43] Except for these, SIRT2, SIRT4, SIRT6, and SIRT7 also play an important role in regulating endothelial cell senescence.^[39] Taken together, sirtuins, have multifaceted roles in the vascular function, are crucial for the maintenance of vascular homeostasis, and are acknowledged as a novel biomarker of vascular aging.

Telomere and telomerase

It is well established that the length of the shortest telomere is a key biomarker of the onset of aging. There is an increasing number of studies demonstrating that telomeres shortened during the aging of human both in cell culture and in normal tissues in vivo.^[44-47] In human, meta-analyses have supported a strong relation between short telomeres and mortality risk of ASCVD, particularly at younger ages.^[48] Telomerase is a reverse transcriptase that adds new DNA onto the telomeres. Recent evidence indicated that vascular aging can be reverted by telomerase activation, and normal physiological aging can be delayed by systemic viral transduction of telomerase.^[49-51] Further insight into the underlining mechanisms of telomerase is, therefore, fundamental for both the prevention and the development of treatment for age-related ASCVD.

Mitochondria and superoxide flashes

Vascular endothelial cells aging exhibit a variety of changes in mitochondrial function, dynamics, and morphology, including decreased membrane potential, increased proton leakage, decreased fusion and division rates, increased species of tricarboxylic acid (TCA)-circulating metabolites, dysfunction of electron transport chain (ETC), overproduction of reactive oxygen species (ROS), and changes in AMP: ATP and ADP: ATP ratios.^[52] Detection of mitochondrial function and morphology is another novel method for evaluation of vascular aging. Interestingly, superoxide flashes are a novel mechanism for quantal ROS production by individual mitochondria, which are triggered by transient openings of the mitochondrial permeability transition pore (mPTP) and are fueled by electron transfer complexes-dependent superoxide production.^[53] A study suggested that superoxide flash is a relatively early and pivotal event of cell metabolism, differentiation, stress response, and aging.^[54]

Nucleolus

Scientists have found that about half of the cells age through a gradual decline in the stability of the nucleolus, which is a region of nuclear DNA where key components of protein are synthesized.^[55] Maintenance of nucleolar homeostasis is suggested to contribute to counteracting

cells aging.^[56] Activation of the NF- κ B pathway by nucleolar stress and induction of apoptosis by nucleolar sequestration of NF- κ B/RelA may emerge as a mechanism of vascular aging.^[57] Further studies are necessary for better understanding the relationship between the nucleolar homeostasis and the process of vascular aging.

cfDNA

The study discovered that the distribution of nucleosomes on the cfDNA (cell-free DNA) strand of healthy young people was regular, while the distribution was scattered in the elderly. Moreover, the cfDNA signal of the two transposons began to decrease with age.^[58] On this basis, cfDNA can be recognized as a new biomarker of aging, and its alternation can be used to clarify the “real age” of organisms and reflect the health status of the body.

Humanin

Humanin is a new member of the polypeptide family encoded by a short open reading frame in the mitochondrial genome. Studies have showed that humanin decreases with age in several species, including humans, and more interestingly, the offspring of centenarians has higher levels of humanin,^[59] which also indicates that humanin is expected to be a new marker for clinical detection of aging in the future.

Ageotype

Recently, scientists have identified four different ageotypes: immunity ageotype, metabolic ageotype, liver dysfunction ageotype, and kidney dysfunction ageotype, by collecting biological samples from 43 subjects, including blood, inflammatory substances, microorganisms, genetic materials, proteins, and byproducts of metabolic processes, and tracking how the samples change over time.^[60] Ageotypes may provide a molecular assessment of aging, reflective of lifestyle and medical history, which may ultimately be helpful in detecting and intervening in the vascular aging process.^[60]

PERSPECTIVES

Vascular aging is a common basis of various ASCVD. In order to delay the process of vascular aging and prevent age-related vascular pathologies, addressing the clinical evaluation of age-related vascular diseases is of critical importance. This review describes the progress of clinical evaluation of vascular aging, including functional evaluation, structural assessment, and cellular molecular biomarkers. Although great progress has been achieved in characterizing aging-induced changes in vascular function, research efforts should persist in this direction to excavate the underlying mechanisms and develop novel methods to evaluate vascular aging, in order for the promotion of

vascular health in older adults. In addition, the construction of comprehensive intervention system based on a risk assessment of vascular aging is the hotspot and direction of future research, which will make it possible to better prevent age-related ASCVD and prolong the lifespan and healthspan of the elderly.

Conflict of Interest

The authors declare no competing interests.

Declarations

The manuscript has been read and approved by all the authors.

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