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GUIDELINES AND CONSENSUS

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Expert consensus on clinical assessment and intervention of vascular aging in China (2018)

Cuntai Zhang[1] | **Jun Tao**[2] | **Cardiovascular Group, Society of Geriatrics, Chinese Medical Association**

[1]Department of Geriatrics, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China

[2]Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China

Correspondence
Cuntai Zhang, Department of Geriatrics, Tongji Medical College of Huazhong University of Science and Technology, No. 13, Hangkong Road, Wuhan, Hubei, 430030, China.
Email: ctzhang0425@163.com
and
Jun Tao, Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University, No. 58, Zhongshan Road, Guangzhou, Guangdong, 510080, China.
Email: taojungz123@163.com

Abstract

With the development of geriatric medicine, more and more reported research has found that as humans grow old, their blood vessels also age. Blood vessels are vital components of various organs. Vascular aging is an important physiological and pathological basis for the aging of organs and systems of the human body and is the common pathogenesis of various chronic diseases in the elderly. Early detection of vascular aging and the use of correct methods to delay and treat vascular aging are of great significance to prevent and control chronic diseases in the elderly and to deal with the increasingly serious problems of population aging. For this purpose, this consensus is formulated for use by geriatric doctors and related personnel.

KEYWORDS

blood vessels aging, practice guideline, pulse wave velocity

1 | INTRODUCTION

With the development of geriatric medicine, more and more reported research has found that as humans grow old, their blood vessels also age. Blood vessels are vital components of various organs. Vascular aging is an important physiological and pathological basis for the aging of organs and systems of the human body and is the common pathogenesis of various chronic diseases in the elderly. Along with the aging of population, the morbidity of vascular-related diseases is extremely high among the elderly.[1] Early detection of vascular aging and the use of correct methods to delay and treat vascular aging are of great significance to prevent and control chronic diseases in the elderly and to deal with the increasingly serious problems of population aging. For this purpose, this consensus is formulated for use by geriatric doctors and related personnel. This consensus mainly introduces the contents of aging of arterial blood vessels.

2 | DEFINITION OF VASCULAR AGING

Morphologically, aging blood vessels represent increased deposition of collagen fibers, increased and disordered elastic fibers, disorganized arrangement of smooth muscle cells, and incrassated intima. Functionally, aging blood vessels show increased stiffness, decreased sensitivity to vasodilator factors, increased sensitivity to vasoconstrictor factors, and decreased angiogenesis. Vascular aging increases the susceptibility of hypertension and atherosclerosis.

3 | MECHANISM OF VASCULAR AGING

Vascular aging is the outcome of the aging of vascular endothelial cells and smooth muscle cells. Cell senescence is regulated by both environment and gene. For the cell itself, two kinds of vascular cells may undergo replicative senescence and induced senescence *in vivo*.

Replicative senescence may be the results of cellular fission caused by vascular damage and repair, while induced senescence may be associated with the accumulation of harmful components in the blood. At the level of vascular tissue, stem cells may be involved in the replacement of damaged and senescent cells. If stem cells are depleted and the self-renewing ability of endothelial cells and smooth muscle cells is depressed, vascular aging may occur.[2]

4 | VASCULAR AGING-RELATED DISEASES

With the aging of the elderly without obvious diseases, the arteries may acquire enlarged lumen, intima-media thickness (IMT), increased vascular stiffness, increased systolic blood pressure, decreased diastolic blood pressure, and increased pulse pressure, which may lead to vascular endothelial dysfunction and other changes in vascular aging. Those changes, occurring earlier than clinical manifestations, are high-risk factors for vascular aging-related diseases, such as atherosclerosis, hypertension, heart, brain, and kidney vascular disease and peripheral vascular disease (PAD). Vascular aging interacts with vascular diseases and provides an environment for the occurrence and development of vascular diseases, which in turn accelerate the process of vascular aging.

4.1 | Early vascular aging

Early vascular aging (EVA) refers to the occurrence of arteriosclerosis and atherosclerosis with earlier age, aggravated degree, and a process faster than the normal aging, which overlap together to accelerate the occurrence and development of vascular aging, leading to early cardiovascular disease (CVD), stroke and PAD,[3] that is, the cardiovascular chain of aging.[4] EVA is an independent predictor of cerebrovascular diseases, cardiovascular death, and all-cause death.

Two standard deviations of age-corrected pulse wave velocity (PWV) values greater than the normal reference values of healthy people are usually used as EVA criteria.[3] A community population study showed that: the incidence of EVA was 12.5%, 26.1% of individuals aged younger than 30 years presented EVA, and it was more common in young men.[5]

During initial visits, the following patients should be evaluated for atherosclerosis: (a) hypertension patients with or without target organs damage, (b) patients with cardiovascular risk factors (family history of early CVDs, diabetes, dyslipidemia, especially familial transmissibility, smoking, etc.), (c) patients with chronic inflammatory diseases (obstructive sleep apnea, chronic obstructive pulmonary disease, chronic inflammatory rheumatism and immune diseases), and (d) patients with chronic renal diseases. In order to achieve early detection, prevention, and intervention for EVA, risk factors (predicting the occurrence of disease: diabetes, dyslipidemia, hypertension, smoking, obesity, mental and/or psychological stress, family history) and risk markers (suggesting the occurrence of disease: microalbuminuria, erectile dysfunction, chronic kidney disease [CKD], carotid intima-media thickness, ankle-brachial involvement, PWV, multi-slice spiral CT coronary angiography, stress test, hypersensitive C-reactive protein, left ventricular diastolic dysfunction in echocardiographic) should be distinguished clearly. Individualized assessment of EVA should be started from 30 years of age. The presence of both risk factors and risk markers indicates EVA; the presence of risk factors but negative risk markers indicates possible EVA; and the absence of risk factors and risk markers indicates no EVA.[4–6]

4.2 | Atherosclerosis

Patients with arteriosclerosis can be associated with vascular aging, and vascular aging can occur in arteries without arteriosclerosis. It is believed that vascular remolding related to vascular aging results in patients being highly sensitive to cardiovascular risk factors (dyslipidemia, diet, hypertension, diabetes, smoking, etc.), which leads to increased likelihood of arteriosclerosis. Vascular aging and atherosclerosis affect each other, form a vicious circle, and finally facilitate the occurrence and development of vascular-related diseases, such as coronary heart disease, hypertension, PAD, cerebrovascular disease, and chronic renal disease.[6]

TABLE 1 Comparisons of atherosclerosis and arteriosclerosis

Differences	Atherosclerosis	Arteriosclerosis (increased vascular stiffness and decreased vascular compliance)
Range of lesion	Focal and obstructive	Diffuse and slowly progressing
Location of lesion	Disease in intima	Disease in media layer
Character of lesion	Inflammatory	Fibrous (decomposed elastin and increased collagen)
Pathological changes	Endothelial dysfunction	Hyperplasia of adventitia and media layer
Risk factors	Related to the oxidation of low-density lipoprotein cholesterol	Related to age and blood pressure
Progress of lesion	Concentric	Eccentric

However, there are some differences between atherosclerosis and atherosclerosis in lesion location, risk factors, pathogenesis, and so on. The comparisons between these conditions are detailed in Table 1.[7]

4.3 | Vascular calcification

Vascular calcification is the deposition of ectopic calcium in vascular sites, a phenotype of vascular aging. An epidemiological investigation showed that 93% of men and 75% of women aged over 70 years had varying degrees of vascular calcification, accompanied with the aging of vascular smooth muscle cells (VSMCs) and the transformation to osteoblast-like cells.[8]

Vascular calcification is divided into vascular intimal calcification and media-layer calcification according to the position of the formation and development of calcified plaques. Media-layer calcification is also called *Monckeberg arteriosclerosis*. Risk factors for media-layer calcification include genetic variation diseases, aging, diabetes, CKD, hypertension, and so forth. The duplication of VSMCs and hyperphosphatemia caused by CKD can induce osteogenic transformation of VSMCs through multiple mechanisms, promote calcium and phosphorus crystals to deposit on elastic fibrous membranes and form solidified calcified plaques, and participate in the destruction and reconstruction of extracellular matrix, resulting in decreased vascular elasticity, increased stiffness, and vascular senescence. Vascular intimal calcification refers to the deposition and development of calcium and phosphorus crystals in the lipid necrosis core of atherosclerotic plaques in patients with atherosclerosis. Some scholars speculate that environmental factors causing vascular intimal calcification are similar to those of media-layer calcification.[9] To some extent, coronary artery calcification scores (CACS) positively correlate with coronary heart disease and various clinical cardiovascular events. The erosion and rupture of unstable plaques caused by atherosclerosis is the main cause of clinical acute cardiovascular and cerebrovascular events. Recently, more and more studies have shown that intimal calcification, which occurs and develops in atherosclerotic plaques, can play an important role in stabilizing the plaques as the degree of calcification deepens. Therefore, there are still many controversies as to whether vascular calcification is the pathological result of body and blood vessels in the aging and pathological environment, or a mechanism of self-compensation and self-protection of the body or blood vessels.

4.4 | Vascular aging-related cardiac changes

Aging can cause left ventricular hypertrophy, atrial fibrillation, and heart-failure-related cardiac changes.[10] The occurrence of left ventricular hypertrophy, one of the risk factors for coronary heart disease, sudden death, stroke, CVD, and left ventricular hypertrophy, increases with age and vascular aging. The hearts of healthy subjects can have the following senescent changes with aging: left ventricular hypertrophy, left ventricular diastolic filling mode, decline of left ventricular ejection and heart rate reserve ability, arrhythmia, and so forth. Vascular aging leads to hemodynamic aging syndrome,[3] including arteriosclerosis and the thickening of the arterial wall, increased systolic blood pressure, and widened pulse pressure; vascular endothelial dysfunction then causes the formation of atherosclerotic plaque in the coronary artery, the decline of coronary blood flow and coronary left ventricular reserve function, followed by deteriorated cardiac function. High blood pressure causes an increase in left ventricular mass, further progressing to left ventricular hypertrophy. An increase in aging-related left ventricular mass and in left ventricular stiffness results in the rise of left ventricular end-diastolic filling pressure, causing heart failure with normal left ventricular ejection fraction. In addition, the increased end-diastolic filling pressure leads to left atrial enlargement and the elevation of left atrial pressure, making the heart prone to atrial fibrillation. Atrial fibrillation shortens the time of diastolic filling, reduces the effect of atrial contraction on left ventricular filling, and thus easily triggers heart failure with normal left ventricular ejection fraction. Therefore, the incidence of left ventricular hypertrophy, atrial fibrillation, and heart failure in elderly people without significant heart disease is significantly higher than that in young people.

4.5 | Hypertension

Interaction between vascular aging and hypertension leads to EVA and arteriosclerosis, which is an independent risk factor for cardiovascular events. Arteriosclerosis and hypertension are mutual cause and effect. On the one hand, hypertension causes damage to the arterial wall, leading to arteriosclerosis. On the other hand, arteriosclerosis itself is the main cause of increased systolic blood pressure, especially in elderly people.[11]

4.5.1 | Vascular aging is the predictor and risk factor for hypertension

Brachial-ankle PWV (baPWV) and carotid-femoral PWV (cfPWV) are associated with elevated systolic blood pressure and hypertension. The increase in aortic stiffness, forward pressure wave amplitude, augmentation index, and carotid stiffness increases the risk of hypertension in the future. The decline in elasticity of large arteries and small arteries is associated with hypertension, suggesting that vascular aging indicators precede and promote the occurrence and development of clinical hypertension.[12]

4.5.2 | Hypertension promotes vascular aging

Age and blood pressure are independently associated with PWV. Blood pressure is an important risk factor for arteriosclerosis. Increased blood pressure leads to increased arterial stiffness. In patients with hypertension who were followed up for 6-year medication, the annual increase rate of PWV was still significantly higher than that in normal blood pressure,[13] indicating that hypertension can accelerate EVA.

4.5.3 | Vascular aging is one of the causes of residual risk of CVD

Niiranen et al[14] pointed out that regardless of whether blood pressure is controlled, most patients with treated hypertension in the community had higher PWV than normal, and the incidence of cardiovascular events remains high. Hypertensive patients treated with antihypertensive drugs still have 50% of residual risk of CVD.

4.6 | Kidney disease

The small blood vessels of the kidney have small resistance and fast blood flow so pulsation could pump more blood into the smallest blood vessels of the kidney, leading to microvascular damage (small artery wall extension, small aneurysm rupture and microthrombosis, etc.), further causing pulse wave nephropathy and resulting in the occurrence of end-stage renal disease.[15]

4.6.1 | Relationship between vascular aging and renal dysfunction in CKD

The increase of each standard deviation of pulse pressure or arterial stiffness causes a drop of estimated glomerular filtration rate/y of 0.15 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ and 0.08 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$, respectively, and the risk of CKD increases by 11% and 13%, respectively. Also, the risk of CKD increases by 7% for the rise of each standard deviation of PWV. These results suggest that the increase of arteriosclerosis index is related to the decline of renal function.[16] Kong et al[17] indicated that every 100 cm/s increase in cfPWV and cfPWV at the highest quartile increases the risk of proteinuria by 15% and 93%, respectively, but this is not related to the estimated glomerular filtration rate.

4.6.2 | Vascular aging is a predictor and risk factor for CVD in CKD

The cfPWV of patients with stage 2-5 CKD is higher than those with hypertension and normal blood pressure. The increase of arterial diameter, arterial stiffness, and arterial wall stress is respectively parallel to the decline of estimated glomerular filtration rate in patients. The degree of aortic sclerosis in patients with CKD is significantly higher than in hypertensive and healthy subjects.[4,18]

Arteriosclerosis is common in end-stage renal disease, and the incidence of plaque calcification is high. Aortic stiffness increases in patients with end-stage renal disease. In patients with mild to severe renal dysfunction, increased central arterial stiffness is related to decreased creatinine clearance.[19] Increased arterial stiffness is an independent predictor of CVD in hemodialysis patients. Arterial stiffness can predict CVD risk and all-cause mortality in patients with CKD undergoing peritoneal dialysis, kidney transplantation, or non-dialysis.[20]

4.7 | Cerebrovascular disease

Vascular aging leads to the development of hemodynamic aging syndrome.[3] Like the mechanism of pulse wave nephropathy, high pulsating blood flow into the small blood vessels of the brain can cause cerebral microvascular damage (small artery wall extension, small aneurysm rupture and microthrombosis, etc.) and cerebral vascular aging, further causing pulse wave encephalopathy and resulting in cerebrovascular disease and cognitive impairment.

4.7.1 | Stroke

The baseline cfPWV in patients with essential hypertension has a predictive value for stroke.[21] Arteriosclerosis is an independent predictor of stroke in healthy subjects.[22] Vascular aging is also a prognostic indicator of stroke. Low cfPWV is associated with a good prognosis for stroke. Aortic PWV in stroke patients can predict asymptomatic coronary artery disease, and its ability to predict is superior to that of traditional risk factors.[23]

Acute ischemic stroke and lacunar infarction are associated with endothelial dysfunction. Cerebral vascular endothelial dysfunction may be an important determinant of acute ischemic stroke and lacunar infarction. Vascular aging may play an important role in the pathogenesis of stroke and may serve as a potential indicator for the risk and prognosis of stroke.[24]

4.7.2 | Vascular aging-related cognitive impairment

Hanon et al[25] reported that the PWV of Alzheimer's disease and vascular dementia were 1330 ± 290 cm/s and 1520 ± 390 cm/s, respectively, which were higher than the control group (1150 ± 200 cm/s), suggesting that arteriosclerosis may be involved in the occurrence and development of vascular cognitive impairment. Increased vascular stiffness is an independent risk factor and predictor of cognitive impairment. PWV in vascular dementia is higher than Alzheimer's disease while endothelial dysfunction may be one of its mechanisms.[26] Cerebrovascular aging plays an important role in the pathogenesis of cognitive disorders, including dementia.[23]

4.8 | Peripheral arterial disease

An increase in arterial stiffness due to vascular aging is a risk factor for PAD and CVD, and a predictor for PAD and cardiovascular and all-cause mortality. Xu et al[27] reported that baPWV is a substitute index for target organ damage and a predictive parameter for PAD. A baPWV > 2100 cm/s is related to potential PAD. Kals et al[28] indicated that small arterial elasticity reduction in patients with symptomatic PAD is a risk factor for independent prediction of all-cause and CVD mortality. Kojima et al[29] also indicated that for patients with sputum index ≤ 0.90, CVD and coronary heart disease risk increase by 2.40 times and 4.13 times, respectively, indicating that vascular aging can predict PAD.

5 | CLINICAL EVALUATION OF VASCULAR AGING

The clinical evaluation of vascular aging is generally divided into two methods: invasive and non-invasive. Invasive evaluation methods include: (a) infusion of acetylcholine in the coronary artery through a catheter measuring changes in arterial vessel diameter and flow reflect vascular endothelial dilation function[30]; and (b) determination of ascending aortic root pressure and central arterial pressure by cardiac catheterization.[31] Because the invasive evaluation method requires complicated equipment, high cost, and certain damage, it is rarely used in clinical practice. The non-invasive methods currently used for clinical evaluation of vascular aging mainly include: (a) Framingham vascular age evaluation formula, (b) non-invasive detection of vascular function and structure, and (c) biological markers of vascular aging cells.

5.1 | Framingham blood vessel age evaluation formula

The Framingham Heart Study revolves around 8491 subjects and was followed up for 12 years. The cardiovascular age formula was established based on risk factors for cardiovascular events, such as male sex, hyperlipidemia, hypertension, diabetes, and smoking. The concept of blood vessel age was proposed and is still widely used today. The assessment of clinical vascular age guides cardiovascular risk prevention, and the Framingham vascular age assessment formula is described in detail in the report by D'Agostino et al.[32]

5.2 | Non-invasive detection of vascular function and structure

5.2.1 | PWV

PWV is the conduction velocity of the arterial pulsation wave from the proximal to the telecentric end along the arterial wall when the heart pumps blood. By measuring the ratio of the distance between the two recorded sites and the pulse wave transit time, the formula is: PWV (cm/s) = L/t, where distance *L* is the distance between the two probes, and propagation time *t* is the time difference between the two waveforms. PWV is based on the mechanism that the conduction velocity of the blood (pulse wave) generated by the heart when the arteriosclerosis is accelerated, and the higher the degree of arterial stiffness, the larger the PWV. With age, the elastic component of the aorta decreases, the wall thickens, the arteries expand progressively, the arterial stiffness increases, and the PWV increases. The central elastic artery increases more with age compared with the peripheral arteries, and PWV is positively correlated with the Framingham score.[33] It has predictive value for the diagnosis of coronary heart disease.[34]

The cfPWV is a gold index for evaluating PWV. However, due to its complicated operation, the baPWV is often used to measure the stiffness of the aorta and middle artery. A greater baPWV value indicates stiffer arteries. According to the change of normal range of different ages and sexes, the baPWV of healthy volunteers under 60 years old in China is less than 1400 cm/s.[35]

5.2.2 | Arterial blood-flow-mediated vasodilation

The principle of vasodilation is to measure the temporal change of the radial artery diameter under the action of shear stress, that is, to fix the inflatable cuff to the forearm (the distal end of the ultrasound probe). Exceeding the systolic pressure for 5 minutes, and then letting off the gas in the cuff, the sudden increase of blood flow in the radial artery after deflation produces shear stress on the vessel wall. This shear stress will activate the production of nitric oxide (NO) in the vascular endothelial cells to release NO. The permeation of NO in the VSMCs causes relaxation of smooth muscle cells to expand the blood vessels, and the diameter change of vasodilation after reactive hyperemia is used as an evaluation index.[36] If endothelial function is impaired, reactive hyperemia stimulates the release of NO from endothelial cells and vasodilation is diminished. Impaired diastolic function of the radial artery is associated with aging, and the diastolic function of the radial artery gradually decreases with age. In males, the decline of brachial artery diastolic function begins to increase after 30 years of age, while the vasodilation function declines in females. The node is 45 years of age.[37] At present, most clinical research data recognize that the normal reference value of brachial artery diastolic function is ≥10%. The higher the vasodilation function value, the better the endothelial function of the subject; the relaxation function of the radial artery < 10% indicates that the endothelial function is impaired (the blood vessel). The lower the diastolic function value, the worse the endothelial function.[38] The calculation formula of vasodilation function = (inner diameter – diameter of tube diameter after arterial hyperemia)/base diameter of tube diameter.

5.2.3 | Intima-media wall

The intima-media wall is the distance between the arterial lumen-intimal interface and the medial-adventitia interface measured by a high-frequency B-mode ultrasound probe. IMT is a landmark structural change in vascular aging. Common carotid artery IMT is an independent predictor of cardiovascular and cerebrovascular risk. For every 0.1-mm increase in carotid IMT, the risk of myocardial infarction in patients can be increased by 11%. In healthy people, IMT gradually increases with age. In people with atherosclerotic cardiovascular risk factors, vascular aging is accelerated and IMT grows faster.

The IMT is measured by taking the proximal sidewall of the common carotid artery bifurcation 1.0-1.5 cm; plaque there indicates disease.

Measurements were made at the proximal end of 1.0-1.5 cm. 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.[36]

5.3 | Cell biology markers

Currently recognized and quantifiable cell markers are endothelial microparticles (EMPs) and endothelial progenitor cells (EPCs). EMPs are microparticles that are detached from the cell membrane of endothelial cells during endothelial cell activation, injury, or apoptosis, and carry certain antigenic properties from endothelial cells. After specific fluorescent antibody labeling, they are detected by flow cytometry and have a diameter of 0.2-1.0 μm CD31 + /CD42- microparticles. The normal value of EMPs in healthy people is less than 1000/μL, and the rise of EMPs represents vascular endothelial injury, suggesting vascular aging.[39]

Endothelial progenitor cells (EPCs) are bone-marrow-derived endothelial cell precursor cells that are present in peripheral blood. However, when vascular endothelial injury occurs, they can be directed to the vascular endothelial injury area to differentiate into mature endothelial cells to repair damaged blood vessels, and activate the surrounding area by paracrine. The endothelial cells promote their proliferation and migration to the injured area for repair. It is an important endogenous vascular endothelial repair mechanism and an important factor in maintaining the balance of vascular endothelial function.[40,41] EPCs can detect the percentage of CD34 + KDR+ cells in peripheral blood mononuclear cells by flow cytometry. Normally, healthy individuals less than 60 years old are not less than 0.13%. Decreased CD34 + KDR+/peripheral blood mononuclear cells are closely associated with the prognosis of atherosclerotic CVD, suggesting vascular aging.[42] At the same time, some protein molecules in the blood may be associated with the aging of blood vessels. Increasing the concentration of FGF21 protein in the blood can delay the aging of the vascular endothelium.[43]

6 | CLINICAL INTERVENTION OF VASCULAR AGING

Vascular aging is both a natural physiological process and a pathological process involving a variety of risk factors. Among them, heredity, environment and lifestyle are involved in the regulation of vascular aging. Strengthening the prevention and control of risk factors of vascular aging and carrying out relevant interventions by regulating the reversible mechanism of vascular aging are effective means for anti-vascular aging at present.

6.1 | Lifestyle improvement

6.1.1 | Diet

A healthy diet is recommended because it is proved to be beneficial to vascular health. Based on 2016 dietary guidelines for Chinese, it is recommended to eat multiple foods and cereal is dominant; eat more vegetables, fruits, milk and soy; eat a proper amount of fish, poultry, eggs and lean meat; decrease the intake of salt and oil and limit consumption of sugar and alcohol. The collocation of various nutrients can refer to the meal plate. The meal plate is divided into four parts: cereal and potato, animal food, vegetables, and fruits. Among them, vegetables and cereal should account for the largest proportion of the area, while animal food, which provides protein, should account for the least.

Calorie-restricted diet is currently the most recognized measure to prolong the life cycle of an organism. The mechanism of calorie-limited diet includes insulin/IGF-1 pathway, sirtuin pathway, TOR pathway, multipath interventions for DNA repair and even intestinal flora.[44] However, there is no effective clinical data in specific clinical practice and the control of calorie intake should be adhered to for a long term.

6.1.2 | Weight control

Obesity is an independent risk factor for vascular diseases.[45] A series of pathological and physiological changes caused by obesity will accelerate vascular aging, so weight control is an important measure to prevent vascular aging. Maintenance of body mass index (≤24 kg/m^2) and waist circumference (<90 cm for men and <85 cm for women) is recommended.

6.1.3 | Smoking cessation

Smoking accelerates vascular aging and is closely related to atherosclerosis, while smoking cessation can reduce the risk of vascular diseases. Everyone can benefit from smoking cessation, so all smokers should be advised to give up.

6.1.4 | Physical activity

Physical activity can improve vascular function and delay vascular aging. Aerobic physical activity benefits blood vessels the most, which can improve arterial compliance, reduce arterial stiffness, and restore vascular elasticity. From a more microscopic perspective, it can mobilize endothelial progenitor cells and enhance the endogenous vascular repair activity of endothelial progenitor cells, thus improving vascular endothelial function and preventing vascular aging. Drug therapy combined with exercise training can improve 6 minutes' walking distance better than drug therapy combined with endovascular treatment.[46] The effects of physical activity on the body come from multiple pathways, including the sirtuin signaling pathway.[47] For the elderly, physical activity must be moderate. In recent years, with the development of rehabilitation medicine, the exercise prescription has attracted more and more attention. Putting forward the individualized exercise prescription according to each person's own characteristics is of great significance to prevent vascular aging. The heart rate reserve method and subjective fatigue grading method can be used to determine exercise intensity combined with subjective feeling. Frequently used aerobic exercises are walking, jogging, cycling, swimming, body building exercise, as well as walking on instruments, treadmills, boating, and so on. It is recommended to start from 20 minutes and gradually increase to 40-60 minutes, with the physical activity frequency of 3-7 times per week.

6.2 | Drug

6.2.1 | Drugs aiming at risk factors

Traditional drugs to treat risk factors have been found to improve vascular function, reduce arterial stiffness, and delay vascular aging, such as blood-pressure-lowering drugs (aimed at hypertension), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, spironolactone, statins, and hypoglycemic drugs of thiazolidinediones.[48]

On the one hand, the anti-vascular aging effects of these drugs are attributed to the benefits of controlling risk factors; on the other hand, some of these drugs can directly improve vascular function and delay vascular aging. Like angiotensin converting enzyme inhibitors, angiotensin receptor blockers can reduce arterial stiffness and improve arterial elasticity more than other antihypertensive drugs. Aldosterone antagonist is not a routine antihypertensive drug, but as an important link in the renin-angiotensin-aldosterone system, its role in protecting blood vessels, improving vascular function, and reducing cardiovascular events is attracting more and more attention. As for statins, in addition to lipid-lowering mechanism, mechanisms like anti-oxidative stress, anti-inflammatory, and mobilization of endothelial progenitor cells to repair vascular endothelial also play a role in anti-vascular aging.

Some new drugs that control risk factors, such as hypertension, hyperlipidemia, and diabetes, have also been shown to play a role in reducing arterial stiffness, treating endothelial dysfunction, and improving vascular reconstruction, which contribute to anti-vascular aging.

6.2.2 | Drugs improving endothelial function

The important pathological basis of vascular aging is vascular sclerosis and endothelial dysfunction. Prostaglandin has the effect of dilating microcirculation, inhibiting platelet aggregation, and improving vascular endothelial. Among these drugs, oral preparation of beraprost sodium and intravenous preparation of alprostadil can bind to IP receptors (7-membrane spanning G-protein coupled receptors that generate cyclic AMP to mediate its physiological effects), increase the synthesis of endothelial nitric oxide synthase, promote the generation of NO, and inhibit formation and secretion of endothelin, thus playing a role in improving the vasodilation of aging blood vessels. Meanwhile, they inhibit apoptosis of endothelial cells, maintain integrity of the vascular wall, and have an effect on improving aging endothelial function.[49] Through the activation of nucleotide cyclase-protein kinase A and nucleotide cyclase-egg-Rap1 pathway, beraprost sodium increases the remoldability of cathepsin K and adhesion structure, thereby enhancing the barrier function of endothelial cells. Beraprost sodium can inhibit proliferation and migration of vascular smooth muscle and improve vascular stiffness. A large number of clinical results show that beraprost sodium therapy reduces the occurrence of vascular events significantly and has the effect of improving vascular aging.[50] The results showed that beraprost sodium had therapeutic effects on patients with intermittent claudication. Beraprost sodium significantly reduced baPWV in patients with coronary atherosclerosis, significantly reduced IMT levels in patients with various CVDs, and significantly improved ankle-brachial index in patients with type 2 diabetes complicated with lower extremity angiopathy.[51] Prostaglandins are endogenous substances in humans, delaying injury of modification and repairing vascular endothelial, with high safety performance. The recommended dose starts at 20 mg/d.

In the condition of vascular endothelial damage, giving exogenous NO or using NO precursors to increase the content of NO will promote the repair of vascular endothelial injury. Nitrosamines are compounds containing nitroso or nitro structure. When L-arginine goes into the body, it can be converted into nitrosamines with the effect of nitric oxide synthase, thus playing a role in protecting and improving vascular endothelial function.

In summary, there are changes in structure and function of aging blood vessels and the accumulation of these changes constitutes the basis of vascular aging. At the same time, vascular aging is the basis of a variety of vascular-related diseases, which seriously threatens human health. Therefore, understanding the mechanism, evaluation index, and management measures of vascular aging will provide a new research target for vascular-related diseases; meanwhile, it contributes to prevention and treatment of vascular-related diseases, improves life quality of elderly patients, and reduces medical costs. Although aging is irreversible, early detection and intervention of vascular aging is a new direction of prevention and treatment of cardiovascular and cerebrovascular diseases.

7 | TASK FORCE FOR THE EXPERT CONSENSUS ON CLINICAL ASSESSMENT AND INTERVENTION OF VASCULAR AGING IN CHINA (2018)

Cuntai Zhang (Tongji Medical College of Huazhong University of Science and Technology [HUST]; Clinical Research Center for Geriatric Disease Prevention and Health Care, Hubei; Clinical Research Center for Treatment and Rehabilitation of Multiple Organ Dysfunction in the Elderly, Wuhan); Jun Tao (Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou); Xiao-Li Tian (School of Life Sciences, Nanchang University); and Hua-Shan Hong (Fujian Medical University Union Hospital).

8 | EXPERTS FOR THE EXPERT CONSENSUS ON CLINICAL ASSESSMENT AND INTERVENTION OF VASCULAR AGING IN CHINA (2018)

Pu-Lin Yu (National Geriatrics Center, Beijing Hospital); Xiao-Ying Li (Department of Geriatric Cardiology, PLA General

Hospital); Lin Wang (Department of Geriatrics, The Second Hospital of Tianjin Medical University); Zai-Jin Jian (Department of Geriatrics, The Second Xiangya Hospital of Central South University).

9 | ADVISORY BOARD MEMBERS FOR THE EXPERT CONSENSUS ON CLINICAL ASSESSMENT AND INTERVENTION OF VASCULAR AGING IN CHINA (2018) (IN CHINESE PINYIN ALPHABETICAL ORDER)

Song Bai (Department of Geriatrics, First Affiliated Hospital of Kunming Medical University); Hong-Liang Cong (Department of Cardiology, Tianjin Thoracic Hospital); Biao Cheng (Department of Geriatrics, Sichuan Provincial People's Hospital); Xu-Jiao Chen (Department of Geriatrics, Zhejiang Hospital); Jin-Fan (Department of Geriatric Cardiology, PLA General Hospital); Ning-Yuan Fang (Department of Geriatrics, Renji Hospital, Medical College of Shanghai Jiao Tong University); Xin-Gui Guo (Department of Cardiology, Shanghai Huadong Hospital); Yi-Fang Guo (Department of Geriatrics, Hebei General Hospital); Hai-Qing Gao (Department of Geriatrics, Qilu Hospital of Shandong University); Xue-Wen Gao (Department of Geriatrics, Inner Mongolia People's Hospital); Qing He (Department of Cardiology, Beijing Hospital); Lu-Lu Han (Department of Geriatrics, Shengjing Hospital affiliated to China Medical University); Hua-Shan Hong (Department of Geriatrics, Fujian Medical University Union Hospital); Xiang Lu (Department of Geriatrics, Second Affiliated Hospital of Nanjing Medical University); Zhan-Yi Lin (Department of Geriatrics, Guangdong General Hospital); De-Ping Liu (Department of Cardiology, Beijing Hospital); Quan Liu (Department of Cardiology, First Hospital of Jilin University); Ze Liu (Department of Geriatrics, General Hospital of Guangzhou Military Command of PLA); Tao Mi (Department of Geriatrics, Tongji Medical College of HUST); Bai-Qing Ou (Department of Geriatrics, Hunan People's Hospital); Wei Qiao (Department of Geriatrics, China-Japan Friendship Hospital); Guo-Xian Qi (Department of Geriatrics, The First Affiliated Hospital of China Medical University); Ming-Zhao Qin (Department of Geriatrics, Beijing Tongren Hospital, Capital Medical University); Yu Song (Department of Cardiology, Tianjin TEDA Hospital); Liang-Yi Si (Department of Geriatrics, Southwest Hospital of Third Military Medical University); Jun Tao (Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University); Xiao-Li Tian (Department of Hypertension and Vascular Diseases, School of Life Sciences, Nanchang University); Ling Tu (Department of Geriatrics, Tongji Medical College of HUST); Zhao-Hui Wang (Department of Geriatrics, Tongji Medical College of HUST); Xiao-Ming Wang (Department of Geriatrics, First Affiliated Hospital of The Fourth Military Medical University); Jin-Hui Wu (Geriatric Center, West China Hospital of Sichuan University); Zhi-Yong Wu (Department of Geriatrics, Hainan Provincial People's Hospital); Hao Xu (Department of Geriatrics, Xiyuan Hospital of Chinese Academy of Chinese Medicine); Di Xu (Department of Geriatrics, Jiangsu Province People's Hospital); Kun Xing (Department of Geriatrics, Shaanxi Province People's Hospital); Yun-Mei Yang (Department of Geriatrics, The First Affiliated Hospital of Zhejiang University); Rui-Ying Yang (Department of Geriatrics, General Hospital of Ningxia Medical University); Cuntai Zhang (Department of Geriatrics, Tongji Medical College of HUST); Guo-Gang Zhang (Department of Geriatrics, Xiangya Hospital of Central South University); Le Zhang (Department of Geriatrics, Tongji Medical College of HUST); Ying-Xin Zhao (Department of Geriatrics, An Zhen Hospital, Capital Medical University, Beijing); Xin Zhu-Ge (Department of Geriatrics, Tianjin Medical University General Hospital); Peng-Li Zhu (Department of Geriatrics, Fujian Provincial Hospital); Zhi-Yu Zeng (Department of Geriatrics, The First Affiliated Hospital of Guangxi Medical University); Min Zeng (Department of Geriatrics, Hainan Provincial People's Hospital); Xiao-Hui Zhou (Department of Geriatrics, The First Affiliated Hospital of Xinjiang Medical University).

10 | SECRETARIES FOR THE EXPERT CONSENSUS ON CLINICAL ASSESSMENT AND INTERVENTION OF VASCULAR AGING IN CHINA (2018)

Lei Ruan (Department of Geriatrics, Tongji Medical College of HUST); Long Chen (Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University).

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CONFLICT OF INTEREST

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