Clinical Interventions in Aging

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REVIEW

Vascular Aging: Assessment and Intervention

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Abstract: Vascular aging represents a collection of structural and functional changes in a blood vessel with advancing age, including increased stiffness, vascular wall remodeling, loss of angiogenic ability, and endothelium-dependent vasodilation dysfunction. These age-related alterations may occur earlier in those who are at risk for or have cardiovascular diseases, therefore, are defined as early or premature vascular aging. Vascular aging contributes independently to cardio-cerebral vascular diseases (CCVDs). Thus, early diagnosis and interventions targeting vascular aging are of paramount importance in the delay or prevention of CCVDs. Here, we review the direct assessment of vascular aging by examining parameters that reflect changes in structure, function, or their compliance with age including arterial wall thickness and lumen diameter, endothelium-dependent vasodilation, arterial stiffness as well as indirect assessment through pathological studies of biomarkers including endothelial progenitor cell, lymphocytic telomeres, advanced glycation end-products, and C-reactive protein. Further, we evaluate how different types of interventions including lifestyle mediation, such as caloric restriction and salt intake, and treatments for hypertension, diabetes, and hyperlipidemia affect age-related vascular changes. As a single parameter or intervention targets only a certain vascular physiological change, it is recommended to use multiple parameters to evaluate and design intervention approaches accordingly to prevent systemic vascular aging in clinical practices or population-based studies.

Keywords: vascular aging, arterial stiffness, endothelial function, arterial wall thickness, therapeutic intervention

Introduction

Our world is turning into an aging society with medical advances and improved social care. The growing elderly population is susceptible to diversified stresses, particularly diseases, and death. With advanced age, vessels degenerate morphologically and physiologically, referred to as vascular aging, contributing to the common cardio-cerebral vascular diseases (CCVDs) in the elderly, such as hypertension, coronary artery disease, aneurysm, and stroke.[1,2] Compared to individuals aged 65–74, the mortality rate of CCVDs increase from 40% to 60% of all deaths in individuals aged ≥80 years.[3] These facts demonstrate the significance of vascular aging to the health of an aging society.

Vascular aging is a developing process characterized by age-related deterioration in both structure and function of blood vessels. It may occur early in individuals with cardiovascular risk factors or diseases, such as abnormal blood chemicals, unhealthy life habits, or hypertension, resulting in early or premature vascular aging that promotes or exacerbates CCVDs.[4] Therefore, early diagnosis and timely therapeutic interventions are key to success in delaying or preventing CCVDs.[5] For this purpose, a few methods have been developed or proposed to detect or intervene in the deleterious changes in vascular structures and functions with age, but their availabilities, including sensitivity and specificity in detection as well as efficacies in the prevention of age-related vascular changes, remain to be evaluated.[4]

In this review, we examine how to assess vascular aging in clinical practices as well as possible interventions available in the literature, providing general guidelines on how to improve the evaluation and prevention of vascular aging in the future.

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Clinical Assessment of Vascular Aging

Vascular Structural Changes with Age

Arterial Wall Thickness

Vascular autopsies show that the arterial wall thickness increases significantly with age due to an increased intima layer, while the load-bearing medial layer has a minor contribution.[6] Other morphological changes have been summarized previously.[7] Despite that many vascular phenotypes are associated with age, the intimal-medial thickness (IMT) is often used to assess vascular aging in clinical practice, as it can be performed non-invasively through ultrasonography.[8–10]

For convenience in practice, the most used artery is the carotid artery. It has been shown that the carotid arterial wall thickness (carotid intimal-medial thickness) in the segment free of plagues increases linearly about 2.5-fold from 30 to 90 years in man.[11,12] The carotid IMT increased about 0.04 mm per decade from ages 40 to 80,[13,14] similar to that in young subjects aged 20–40.[15,16] Other arteries, such as common femoral arteries, superficial femoral arteries, popliteal arteries, and brachial arteries, are also used to measure age-dependent wall thickening.[17,18]

Unlike other parameters used to evaluate vascular aging, the wall thickening of vessel segments free of atherosclerotic plaques, represented as IMT (or carotid IMT), appears very consistent with the chronological ages,[19] thus, it potentially represents the physiological vascular aging.[11,18]

Histomorphological and ultrasonographic observations of IMT in arteries are presented in Figure 1.

Arterial Lumen Diameter

An increase in arterial lumen diameter is reported in aged vessels, likely due to the repeated stretch of the elastic arteries through an entire lifetime, causing elastin fatigue, and thus leading to elastin fracture and fragmentation.[20,21] Loss of elastin contributes to the enlarged lumen diameter mostly in the proximal aorta.[21] Transthoracic echocardiography is commonly used to measure the diameter of the aortic root at multiple locations, for instance, the aortic annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta, to obtain reliable results.[22]

Previously, the Framingham Heart Study established a reference value for aortic root diameter by using M-mode echocardiography, based on a large healthy population. They observed that aortic root diameter constantly increased (from 28–33 mm to 33–37 mm) with age from 25 to 75 years, although the age-dependent dilation varies in the subjects with different body surface areas (BSA).[23] In a B-mode echocardiography-based study, however, BSA is the most important determinant of aortic root diameter at the aortic annulus and sinuses of Valsalva, while age is mainly associated with the aortic root diameter at ascending aorta.[24] Other B-mode echocardiography-based studies showed that the association between diameter at the aortic annulus and age was weak,[25] while the diameter of the ascending aorta is more closely related to age.[26] Methodologically, the aortic root diameter measured by B-mode echocardiography is larger than that measured by M-mode echocardiography.[24] Therefore, when comparing the results from different studies, it is critical to consider the influence of different imaging techniques and measurement positions on the value of aortic root diameter.

A study reported that aortic root diameter steadily increases with age from 15 to 64 years after the adjustment for BSA.[27] This finding is consistent with another Caucasian population-based study, which reported an increase of 1.1mm and 0.9mm in the diameter of the sinuses of Valsalva and ascending aorta per decade in people 15 years and older.[28] The correlation between age and aortic root diameter is non-linear. The age-dependent dilation of aortic root was faster in children under age 15 than adults, with a rate of nearly 10 mm per decade (age, 1–15) versus 1.1 mm per decade (age>15). Importantly, BSA, rather than age, was the most decisive factor in aortic root dilation in those under 15 years.[24,28] These studies pointed out that the diameter of ascending aorta assessed by echocardiography is more closely related to aging.[26] Age-related aortic root dilation usually occurs in the adult population, as the aortic dimensions in those younger than 15 are mainly affected by body size.[24,28]

In addition to the aorta, the positive association between arterial lumen diameter and age was also shown in peripheral arteries such as brachial arteries,[29] popliteal arteries,[18,30] femoral arteries[18,31] as well as carotid arteries.[32,33] These suggest that an increased arterial lumen diameter is a good indicator for vascular aging. Vascular structural changes with ages are summarized in Table 1.

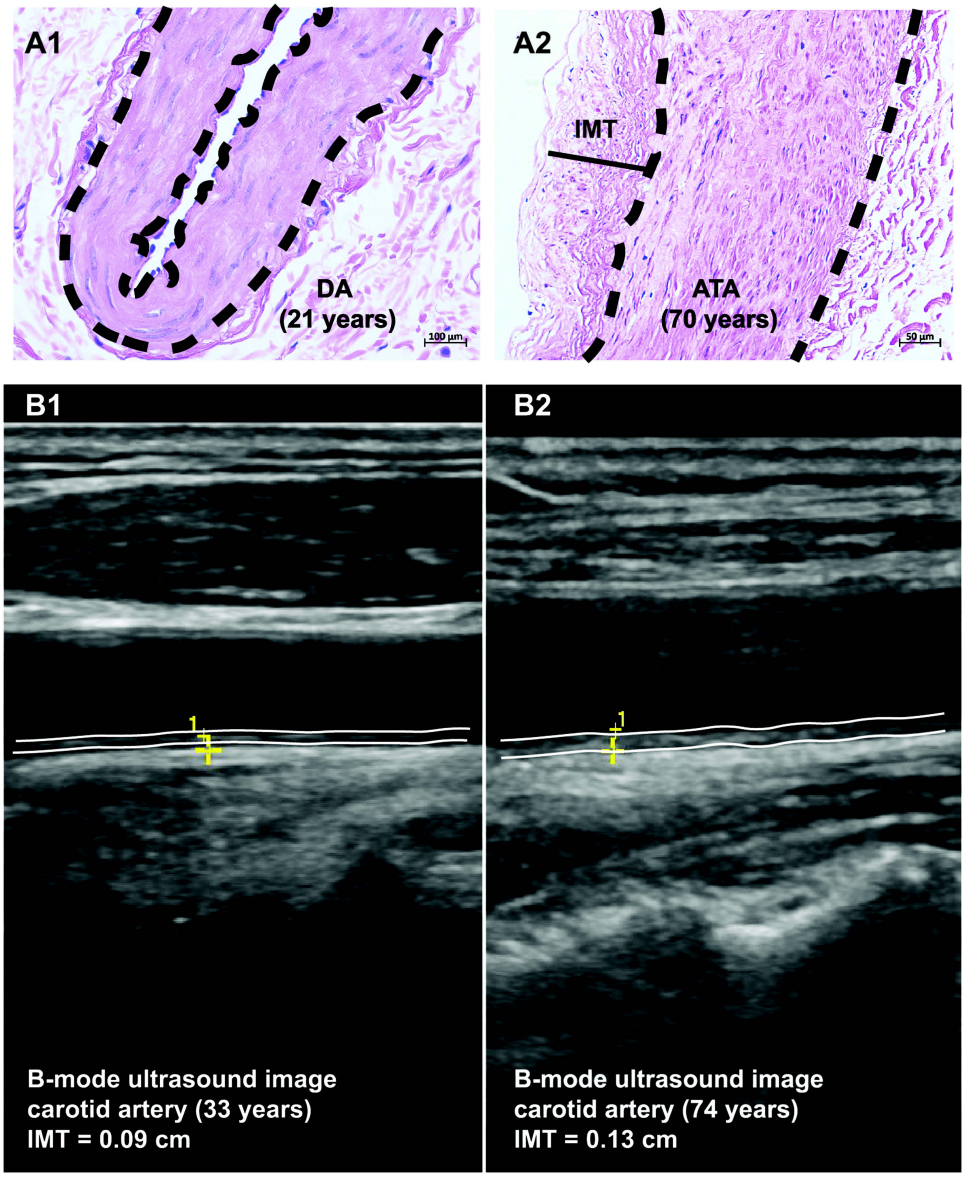

Figure 1 IMT in young and old arteries. The hematoxylin-eosin staining of tissue sections from digital artery (DA, 21-year old, (**A1**)) and anterior tibial artery (ATA, 70-year old, (**A2**)). Tissues were obtained from male patients who had radical surgeries for polydactyly and malignant melanoma of lower extremity, respectively, sectioned at 4 micrometers, and fixed with 4% polyformaldehyde for 24 hour prior to staining. The IMT was only measured and pointed in ATA and the tunica media layers were labeled with dash lines as IMT was too thin to be measured accurately. (**B1** and **B2**) are B-mode ultrasound images of carotid arteries from two male patients at the ages of 33 (IMT = 0.09 cm) and 74 year (IMT = 0.13 cm). The intimal-medial layers were labeled with dash lines. The positions for measuring IMT were pointed with yellow crosses.

Vascular Functional Changes with Age

Endothelium-Dependent Vasodilation

Endothelium-dependent vasodilation loses sensitivity with advancing age in response to dilators, such as acetylcholine; therefore, it can be considered as a functional parameter for the degree of vascular aging. Age-related endothelial dysfunction has been documented in coronary arteries,[34] peripheral arteries,[35] and microcirculation.[36] The underlying mechanisms are multifactorial, including increased oxidative stress, inflammation response, and unbalanced release of vasoconstrictors and vasodilators.[35,37,38]

Acetylcholine-Induced Vasodilation

Intracoronary infusion of acetylcholine induces dilation of healthy coronary arteries by stimulating endothelial cells to release nitric oxide (NO).[39] Therefore, quantitative angiographic analysis of acetylcholine-induced coronary atrial

Table 1 Aging-Related Vascular Structural Changes on Clinical Assessment

Aging-Related Vascular Indicators	Arteries	Major Findings	Ref
Arterial wall thickness (IMT)			
	Carotid arteries	The IMT of carotid arteries increased about 2.5-fold from 30–90 years old, with a rate at 0.04 mm per decade	[11–16]
	Superficial arteries	The IMT of superficial arteries increased about 1.5-fold from 30–60 years old.	[17]
	Femoral arteries	The IMT of femoral arteries increased about 1.25-fold from 20–70 years old.	[18]
	Popliteal arteries	The IMT of popliteal arteries increased 0.2 mm from 20–70 years old.	[18]
	Brachial arteries	The IMT of brachial arteries increased 0.15 mm from 20–70 years old.	[18]
Arterial lumen diameter			
	Aorta	The diameter of aorta increased 10 mm per decade from 1–15 years old. Then, the rate decrease to 1.1 mm per decade in the sinuses of Valsalva after 15 years old.	[24,27,28]
	Brachial arteries	The diameter of brachial arteries increased 1.25-fold from 30–50 years old at the proximal site.	[29]
	Popliteal arteries	The diameter of popliteal arteries increased 25% from 25–70 years old.	[30]
	Femoral arteries	The diameter of femoral arteries increased 12% and 21% in male and femoral from 25–67 years old, respectively.	[31]
	Carotid arteries	The diameter of carotid arteries increased 24% from 20–80 years old and the age-dependent dilation is faster after the fifth decade.	[32]

dilation is used as the "gold standard" to detect coronary endothelial function. Existing studies demonstrate a positive correlation between aging and declined coronary blood flows upon acetylcholine infusion into the left main coronary artery. The ratio of acetylcholine-induced and papaverine-induced percentage change of blood flow declined by nearly 80% from ages 20 to 80.[34,40–42] The acetylcholine-induced vasodilation is dependent on dosages, particularly low dosages. It has been reported that vasodilation was decreased by 2.5, 2.6, and 4.1mm per decade at the dosages of 1, 3, and 10 μg/min, respectively.[34] A general illustration of acetylcholine induces dilation is shown in Figure 2A.

The disadvantages of using the intracoronary infusion of acetylcholine to assess vascular dilation are its invasive nature and high cost, therefore, it is only used in patients undergoing angiography. Under this consideration, peripheral arteries, such as the brachial arteries and cutaneous microcirculation are examined instead of the coronary artery.[35,43] For

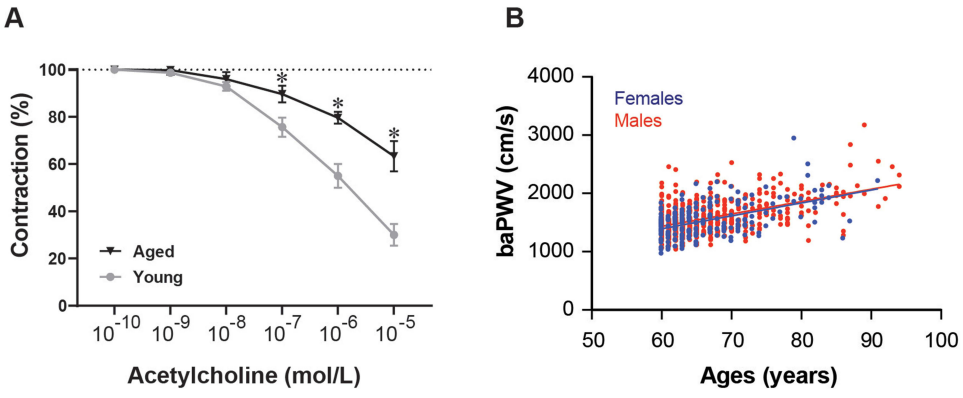

Figure 2 Functional shift with increased ages. (**A**) Endothelium-dependent vascular relaxation induced by acetylcholine for the artery rings from young and old man. The cumulative concentration response curves were recorded, and statistical significance was indicated with asterisks (*). (**B**) brachial-ankle pulse wave velocity (baPWV) was measured in men (red) and women (blue) at ages from 60 to 95 years. The baPWV is increased with ages but not different between genders.

example, studies show that the endothelium function of the brachial artery in response to acetylcholine, represented as forearm blood flow, similar to the coronary artery.[35,44] The infusion of acetylcholine into the brachial artery led to a decrease of nearly 40% in maximum dilation of healthy subjects aged 20–80.[35]

Reactive Hyperemia-Induced Vasodilation

During reactive hyperemia, a dramatic increase in arterial blood flow results in vasodilation.[45] This process also depends on the increased release of NO from endothelial cells.[46] Flow-mediated dilation (FMD), an endothelial-dependent (primarily NO-mediated) dilation of conduit arteries in response to an abrupt rise in blood flow and shear stress, is the widely used method to measure conduit artery endothelial function. Reactive hyperemia-induced vasodilation can also be presented as reactive hyperemia index measured by reactive hyperemia-peripheral arterial tonometry. Both FMD and reactive hyperemia index are noninvasive assessments of endothelial functions and vascular aging.[47]

FMD is largely attenuated in the elderly.[48–51] Studies have shown that the FMD of the elderly (age>70) is nearly 50% lower than that of the young (age<30).[48–51] Different from IMT or diameter discussed above, the age-related decrease of FMD is not linear. The decline in FMD is not much changed in the group with ages 24 to 39 years[15] but becomes pronounced in men above 40 years and women above 45 years of age.[52,53] The decrease rate is reported to be 0.21% and 0.49% per year in men and women, respectively.[53] The sexual dimorphism in FMD is likely due to the vasoprotective effects of estrogen. Therefore, it is better to use FMD as a predictor of vascular aging in men over 40 and women over 50.

Arterial Stiffness

Arteries become rigid with aging, attributed to both structural and functional alterations.[54] Arterial elasticity is strongly affected by the intimal layer and medial layer of the vascular wall.[55] First, the stress-bearing elastin fibers fracture and collagen fibers deposit in the medial layer, and the ratio of elastin to collagen decreases.[56] Then, the increase in vascular wall pressure leads to a phenotypic switch of smooth muscle cells, resulting in excessive proliferation and migration of smooth muscle cells, as well as the production of more extracellular matrix.[57] Finally, endothelial dysfunction causes a diminished synthesis and release of vasodilators, and endothelial cells become super sensitive to vasoconstrictors while insensitive to vasodilators.[37,38] Together, arterial elasticity decreases with ages that impairs the cushion function of arteries. The stiffened arteries is not able to buffer cardiac output, which causes quicker propagation and reflection of pulse waves.[21]

Pulse Wave Velocity

Pulse wave velocity (PWV) measures the velocity of a pulse wave traveling between two arterial sites, based on the principles of applanation tonometry. When arterial elasticity decreases, the pulse wave propagates rapidly along the vasculature, which is manifested as increased PWV.[58] It can be performed in various arterial segments, such as carotid-brachial arteries, brachial-ankle arteries, and carotid-femoral arteries. Among these, the carotid-femoral PWV (cfPWV) is often used as it is easy to measure, closely correlated with central arterial stiffness, and has the most clinical relevance.[59–61]

The cfPWV was reported to increase by about 2.5-folds from the age of 21 to 96 years in subjects from the Baltimore Longitudinal Study of Aging.[62] Another study in a Chinese-population showed that the cfPWV was increased by 83% from 2-month-old infants to 90-year-old elderly.[63] The association between increased cfPWV and age is not linear, as cfPWV increases more rapidly after the fifth decade.[54,64,65] Similar findings were reported in the different cohorts.[66]

It is noteworthy that age-related arterial stiffness is regionally heterogeneous and is influenced by blood pressure.[63,64,67] It has also been reported that the carotid-brachial PWV is weakly correlated with age,[64] but another arterial stiffness index, brachial-ankle PWV (baPWV) shows a strong correlation with ages, similar to the cfPWV.[66,68,69]

To better understand the age-related changes of PWV, a baPWV in Chinese men and women from ages 60–90 is presented (Figure 2B).[70]

Augmentation Index

The augmentation index (AIx) is determined by pulse wave reflection and represented as a surrogate parameter for arterial stiffness.[71] As the conduit artery loses its elasticity, the reflected wave from the impedance mismatch returns earlier, which reaches to the central aorta in the late systolic period and merges with the systolic blood pressure. This process leads to an increment in aortic systolic blood pressure.[72] Accordingly, aortic AIx, which measures the contribution of the early reflected waveform to the late increased systolic blood pressure in ascending aorta, is considered to be another indicator of systemic arterial stiffness.

Although PWV and AIx are both used to measure arterial stiffness, they provide different information about arterial properties and are not interchangeable.[73,74] AIx is primarily affected by two factors, the wave propagation velocity (PWV) and the distance between the aortic root and major impedance mismatch sites. Thus, AIx is not only an indicator that reflects arterial stiffness.[73] For this reason, the age-related changes of AIx are not fully consistent with changes in PWV.

As we mentioned earlier, cfPWV persistently increases with ages (from 2 months to 90 years old).[63] However, studies have shown that AIx is markedly higher in young children, and gradually declines with ages until adolescence (15–18 years) while the cfPWV increases slowly.[75,76] Therefore, the higher AIx in children is likely attributed to the short length of the aorta rather than the accelerated wave reflection. After puberty, AIx is reported to be positively associated with age. In a large, healthy cohort, it was shown that AIx increases nearly 5-fold from adolescents aged 20 to the elderly aged 96.[73] Like the cfPWV, the increase of AIx with age is non-linear.

Previous studies demonstrated that cfPWV increases more significantly in subjects aged 50 and above, while AIx increases more prominently in subjects under 50 years old.[54,64] The increase of AIx in the elderly is likely attenuated due to the reversal of the central-to-peripheral arterial stiffness gradient.[64] Central arterial stiffness consistently increases with age, and ultimately exceeds peripheral arterial stiffness in the elderly.[64] This change shifts the reflecting point distally, thereby reducing AIx increments. There are two turning points for age-related changes in AIx. It first occurs in adolescence when the age-related decrease in AIx stops and turns into an age-related increase, then during middle age when the increment rate of AIx diminishes.[66,77]

Thus, AIx is more likely to be an indicator of age-related arterial stiffness in people aged over 18, whereas cfPWV reflects the course of age-related arterial stiffness across lifespan.

Other Methods to Detect Arterial Stiffness

Recent studies have proposed a novel A-mode ultrasonic technique named ARTerial Stiffness Evaluation for Non-invasive Screening (ARTSENS). It is an image-free device for measuring arterial wall thickness based on Gaussian-mixture modeling.[78,79] More than a dozen of published articles have claimed the advantages of ARTSENS in clinical applications, including its portability, high-throughput, and efficiency in evaluating vascular wall and stiffness, but a large cohort-based clinical trial has yet to yield any conclusive results.[80–83] Vascular functional changes are listed in Table 2.

Laboratory Tests and Indirect Measurements of Vascular Aging

In addition to an assessment of age-associated vascular structural and functional alterations by using complex and expensive devices, the measurement of blood biomarkers is another way to indirectly evaluate vascular aging. In the following section, we will highlight several frequently used biomarkers.

Endothelial Progenitor Cells

Endothelial progenitor cell (EPC), the precursor of endothelial cell, is thought to be originated from bone marrow.[86] EPCs are recruited to the site of injury where they differentiate into endothelial cells, thereby regenerating damaged endothelium.[87–90]

The number of EPC colonies has been identified as an independent predictor of FMD. The EPC colonies were approximately 3-fold higher in subjects with a higher FMD than those with a low FMD.[91] Moreover, EPCs are correlated with arterial stiffness and arterial elasticity.[92] In addition to counting the number of EPCs, the changes of EPCs in their functions are associated with vascular aging as well. The proliferative and migratory capacity of EPCs is linearly reduced with the increases of baPWV.[93] The

Table 2 Aging-Related Vascular Functional Changes on Clinical Assessment

Aging-Related Vascular Indicators	Arteries	Major Findings	Ref
Acetylcholine-induced vasodilation			
	Coronary arteries	The vasodilation of coronary arteries decreased about 80% from 20–80 years old.	[34,40–42]
	Cutaneous microcircula-tion	The vasodilation of cutaneous microcirculation is 75% lower in old people (aged 61) compared with young group (aged 27).	[43]
	Brachial arteries	The vasodilation of brachial arteries decreased about 40% from 20–80 years old.	[35]
Flow-mediated vasodilation (FMD)			
	Brachial arteries	The FMD of brachial arteries decreased about 50% from 20–80 years old.	[49–51]
		The FMD of brachial arteries remain steady from 24–39 years old.	[15]
		The FMD of brachial arteries decreased 2.1% and 4.9% per decade in men above 40 years old and women above 45 years old, respectively.	[52,53]
	Popliteal arteries	The FMD of popliteal arteries is 50% lower in old people (aged 60–79) compared with young people (aged 20–30).	[84]
	Femoral arteries	The FMD of femoral arteries is 38% lower in old people (aged 69) compared with young people (aged 22).	[85]
Pulse-wave velocity (PWV)			
	Carotid-femoral arteries	The PWV of carotid-femoral arteries increased 2.5-fold from 21–96 years old.	[62]
		The PWV of carotid-femoral arteries increased 83% from 2-month-old infants to 90 years old elderly.	[63]
		The PWV of carotid-femoral arteries increased more rapidly after the fifth decade.	[54,64–66]
	Carotid-brachial arteries	The PWV of carotid-brachial arteries is weakly associated with age.	[64]
	Brachial-ankle arteries	The PWV of brachial-ankle arteries increased 25% from 20–70 years old and it shows a strong correlation with age.	[66,68,69]
Augmentation Index (AIx)			
	Aorta	The AIx decreased with age from young children to adolescence (15–18 years)	[75,76]
		The AIx increased with age after puberty. It increased about 5-fold from 20–96 years old.	[73]
		The increasing rate of AIx slows down after the fifth decade.	[54,64]

age-dependent increase in carotid IMT is negatively associated with EPC function, and the survival rate of EPCs from the elderly who have high carotid IMT is decreased significantly in a healthy population-based study.[94] Accordingly, EPCs appear to be a surrogate biomarker for predicting vascular aging.[95]

Telomere Length

Telomere is located at the end of each eukaryotic chromosome to maintain genetic integrity. When the telomere length shortens to critical region, the cell permanently loses its ability to divide and enters senescence.[96] Thus, telomere attrition is considered a hallmark of replicative senescence or chronological aging, and it is also involved in some premature or accelerated aging.[97,98]

Blood leukocyte telomere lengths (LTL) are closely related to carotid IMT and cfPWV, therefore, LTL serves as an indirect marker of vascular aging. The correlation of LTL with carotid IMT has been tested in healthy elderly populations free of cardiovascular diseases[99] as well as in hypertensive and diabetic patients.[100–102] LTL is negatively correlated with cfPWV after excluding known confounding factors such as gender, menopausal status, blood pressure, blood glucose, and lipid level,[103,104] therefore, considered as a better indicator of biological aging in vasculature than chronologic age in patients with cardiovascular damage.[105]

Advanced Glucagon End Products

Advanced glycation end-products (AGEs) are heterogeneous compounds formed by the non-enzymatic glycosylation reactions between reducing sugars and the amino group of proteins.[106] They are accumulated in the vascular wall during aging and contribute to arterial stiffness by cross-linking with collagen fibers.[107] Endothelial cells, on the other hand, express receptors for AGEs (RAGEs). Activation of AGEs-RAGEs signaling elicits vascular inflammation and oxidative stress, which ultimately leads to endothelial dysfunction.[108] RAGEs can be cleaved into a soluble form, soluble RAGEs, which lack a membrane-anchoring domain; therefore, it circulates in the blood.[109] Binding of soluble RAGEs to AGEs acts dominant-negatively, neutralizing the deleterious effects of AGEs on vessels.[110,111] Elevated circulating levels of AGEs were independently associated with increased arterial stiffness in healthy individuals as well as in diabetic and hypertensive patients.[112–114]

An accelerated age-dependent increase in cfPWV has been reported in subjects with low circulating soluble RAGEs.[115] Based on these findings, the combination of the AGE-soluble RAGE should provide more enriched information than a single parameter in evaluating vascular aging.[110,116] Supportively, the ratio of skin-deposited AGEs to soluble RAGEs is a better predictor of arterial stiffness than that in blood.[116–118]

C-Reactive Protein

C-reactive protein (CRP) is an inflammation biomarker that is linearly correlated with cfPWV, forearm blood flow, and AIx.[119–121] Serum CRP levels of elderly populations without overt CCVDs are increased with cfPWV,[122,123] and AIx is increased by about 35% from 0.6 mg/L to 3.6 mg/L of CRP.[124–126]

It is important to know that a single assessment of CRP concentration is unlikely to provide credible information as CRP levels are susceptible to other factors such as age, gender, and infection.[127] However, the cumulative CRP is shown to be a reliable marker in the prediction of arterial stiffness.[127,128] To sum up, those cellular and molecular markers that associated with age-related vascular structural and functional changes are presented in Table 3.

Table 3 Cellular and Molecular Markers of Vascular Aging

Markers	Association with Aging-Related Vascular Indicators	Ref
EPC		
EPC numbers	EPC numbers is positively associated with FMD EPC numbers is negatively associated with radial PWV	[91,92]
EPC function	EPC function is negatively associated with baPWV, carotid IMT	[93,94]
Telomere length		
LTL	The LTL is negatively associated with carotid IMT, cfPWV	[99–101,103,104]
AGEs		
Circulating AGEs	The circulating AGEs is positively associated with cfPWV	[113,114]
Soluble receptors for AGEs	The soluble receptors for AGEs is negatively associated with cfPWV	[115]
Skin AGEs/Soluble receptors for AGEs	The Skin AGEs/Soluble receptors for AGEs is positively associated with cfPWV	[116]
CRP		
Single CRP concentration	The single CRP concentration is positively associated with cfPWV, AIx The single CRP concentration is negatively associated with acetylcholine-induced vasodilation	[121–126]
Cumulative CRP exposure	The cumulative CRP exposure is positively associated with cfPWV, baPWV	[127,128]

Interventions for Vascular Aging

Pharmacologic Interventions

Anti-Hypertensive Agents

Hypertension is prevalent in the elderly and bring a huge burden for the society. It is a predominant risk factor that facilitates age-related changes in vascular function and structure.[129] The cfPWV is accelerated in hypertensive patients with 0.93m/s per decade, compared with 0.44 m/s per decade in normotensive patients.[130] The maximum forearm blood flow in response to acetylcholine decreased by nearly 42% in hypertensive patients.[131] Furthermore, elevated blood pressure increases tension on the vascular wall, exacerbating vascular wall remodeling.[20]

Anti-hypertensive drugs are effective treatments to halt the progression of vascular aging. Here, we discuss five of the most commonly used antihypertensive drugs, including renin–angiotensin II-aldosterone system inhibitors (ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers, AdRB: aldosterone receptor blockers), calcium channel blockers (CCB), β-receptor blockers, and diuretics on vascular aging.

It has been reported that all anti-hypertensive treatments, including ACEI, CCBs, β-blockers, and diuretics effectively reduced blood pressure; however, only ACEI improved endothelium-dependent vasodilation in randomly selected hypertensive patients treated with monotherapy.[132] Supportively, in a meta-analysis, ACEI was reported to be more effective in enhancing endothelial function against all other drugs administered as a monotherapy in hypertensive patients.[133] Another study reported that both ACEI and ARB improved FMD in hypertensive patients compared to β-blockers and CCB.[134] These suggest that inhibition of the renin–angiotensin system is better for the improvement of endothelium-dependent vasodilation.

On the other hand, it was found that ACEI, CCB, β-blocker, and diuretics alleviate arterial stiffness in the long-term treatment compared with the control group. There was no significant difference in therapeutic effects among these groups.[135] Other studies also reported that ACEI and ARB do not exhibit superiority in alleviating arterial stiffness compared with other types of antihypertensive treatments.[136–140] ACEI effectively improved arterial elasticity in hypertensive patients compared with control groups but found no significant extra benefit compared with other types of anti-hypertensive drugs.[141]

Unlike ARB, AdRB, or CCB, diuretics exhibit only a moderate effect on vascular stiffness.[142,143] Studies showed that ARB (losartan) and diuretics (chlorothiazide) both reduced blood pressure to normal levels in hypertensive patients after 4 weeks of treatment, while only losartan led to a significant decrease in cfPWV and AIx,[144] while both AdRB (eplerenone) and CCB (amlodipine) were effective in reducing cfPWV with no significant difference between the two groups.[139] It was further reported in the EXPLOR trial that ARB (valsartan), not β-blocker (atenolol), significantly decreased cfPWV after adjusting for blood pressure and heart rate.[145] Atenolol improves arterial elasticity, however, it increases AIx attributed to the lower heart rate.[146] The third generation of β-blockers, such as nebivolol and carvedilol, showed better results in the prevention of vascular aging. For example, nebivolol significantly reduces AIx.[147] Further, with the infusion of nebivolol into the iliac artery, arterial elasticity was reported to improve only using nebivolol.[148] Even if β-blockers reduce cfPWV to the same extent as ACEI or ARB does, the latter causes a long-lasting reduction in cfPWV.[149,150]

Treatment for Diabetes

Hyperglycemia, a feature of patients with diabetes or impaired glucose metabolism, contributes to vascular aging.[151] Hyperglycemia can facilitate AGEs formation and endothelial cell senescence,[152,153] which in turn aggravate arterial stiffness and endothelial dysfunction.[112] Compared with age-matched healthy subjects, FMD is reduced by approximately 14% in newly diagnosed diabetic patients.[154] The endothelium function is inversely correlated with the severity of diabetes and blood glucose levels.[155] In addition, the age-dependent increase of arterial stiffness and arterial wall thickness is accelerated in diabetic patients.[156–158] Therefore, anti-hyperglycemic treatment should be considered in the prevention of vascular aging.

Metformin is the first line of treatment for diabetes, as it re-sensitizes patients to insulin. It also improves age-related vascular function significantly.[159] It has been reported in the REMOVAL trial that the age-related carotid IMT increase was reversed with a 0.012mm/year reduction in diabetic patients treated with metformin for 5 years.[160] The percentage

changes in coronary blood flow in response to acetylcholine were increased by 75% after 6 weeks of metformin treatment in pre-diabetic patients compared with the non-treated group.[161] Moreover, FMD and reactive hyperemia index were increased by 1.8-fold and 1.3-fold, respectively, after 12-week treatment with metformin in type-2 diabetic patients.[162] Metformin also improves AIx, cfPWV, and endothelial-dependent vasodilation in polycystic ovary syndrome patients treated with metformin for 8 weeks.[163]

Other anti-diabetic agents, such as peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist (Thiazolidinediones), such as pioglitazone, troglitazone, and rosiglitazone, and sodium-glucose co-transporter-2 inhibitor, such as dapagliflozin, empagliflozin, and pioglitazone, similar to Metformin, can improve age-related vascular phenotypes. A study reported that carotid IMT was decreased by 0.08 mm in diabetic patients treated with troglitazone for 3 months, whereas increased by 0.016 mm in placebo-treated subjects.[164] Notably, the carotid IMT increased by 0.031 mm after 48 weeks of placebo treatment, and decreased by 0.012 mm after 48 weeks of rosiglitazone treatment in those with normoglycemia, although there was no significant change in fasting blood glucose level after treatment.[165,166] Thus, the effect of thiazolidinediones in delaying vascular aging is at least in part independent of its hypoglycemic ability.[167]

Sodium-glucose co-transporter-2 inhibitor block glucose re-absorption in the proximal renal tubes and accelerate glucose excretion.[168] Empagliflozin improves endothelial function to the same extent as metformin does, however, it showed superior benefits in reducing cfPWV in type 1 diabetic patients.[162] Dapagliflozin improves FDM even when the treatment lasts as short as two days in type-2 diabetic patients[169] and is more efficient than hydrochlorothiazide.[170]

Similar to thiazolidinediones, sodium-glucose co-transporter-2 inhibitor mediated restoration of vascular function is not fully dependent on their abilities to reduce glycemia and blood pressure.

Sulfonylureas appear to have little effect on improving vascular function in diabetic patients.[171–178]

Glucagon-like peptide-1 seems to ameliorate endothelial function through its indirect mechanism in improving glucose and lipid metabolisms.[179] Exenatide, a glucagon-like peptide-1 analog, has been proven to improve brachial FMD in diabetic patients after long-term administration.[180,181] Besides, even single dose of exenatide had favorable effects on endothelial function over two sequential meals in diabetic patients.[182,183] Moreover, chronic administration of exenatide can also improve cfPWV,[184,185] AIx[179] and carotid IMT in people with type 2 diabetes mellitus.[186]

Intensive insulin therapy has been reported to improve acetylcholine-induced vasodilation in patients with type 1 diabetes.[187] In addition, it has been shown that endothelial function is better in type 2 diabetes patients with insulin therapy combined with metformin, compared with metformin monotherapy.[188,189] However, there are debated results which demonstrate that FMD in diabetic patients is not increased after 14 weeks of insulin glargine therapy.[179]

Lipid-Lowering Agents

Hyperlipidemia directly damages endothelial cells and EPCs impeding their abilities to repair the injured endothelium.[190] Both carotid IMT and cfPWV are increased in patients with familial hypercholesterolemia than in normal people,[191–193] suggesting that patients with hyperlipidemia suffer from premature vascular aging.

3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) inhibitors, also known as statins are widely used in the treatment of hyperlipidemia. Statins improve blood profile and restore vascular structure and function.[194–196] However, it is still under heat discussion that whether the improvement of endothelial function is due to its lipid lowering effects or through its arterial pleiotropic effect. Some studies raise that statin therapy has pleiotropic effects because it can improve endothelial function in such a short time when the lipid-lowering effect of statins is incomplete,[194] while recent studies that combine simvastatin treatment with ezetimibe to reach a lower LDL-C level suggest that the improvement of endothelial function is more correlated with the reduction of lipid level.[197,198] Besides, researches focusing on the effects of statin therapy in ameliorating arterial stiffness have produced mixed results.[199–202] It is also discovered that the improvement of arterial stiffness index may be transient under statin therapy.[203] Patients with chronic kidney diseases possess lots of cardiovascular risk factors, and manifested as premature vascular aging.[204] One study investigating the effects of statin in restoring arterial stiffness in patients with chronic kidney diseases has found that statin may retard the progression of arterial stiffness.[205]

It was found in a longitudinal study that the aortic root diameter was decreased in hypercholesterolemia patients treated with atorvastatin for two years.[206] Other studies revealed that a low dose of simvastatin only moderately reduced

the LDL-cholesterol level (25%) but did not reduce carotid IMT values, while high doses of atorvastatin largely reduced the LDL-cholesterol (45%) concentration, and reversed the age-related progression of carotid IMT.[195,196] These indicate that structural improvements of arteries require more intensive and longer statin treatments.

Non-Pharmacologic Interventions

Physical Activity

It has been reported in a Spanish cross-sectional study that vascular aging was positively correlated with sedentary time but inversely related to physical activity.[207] The arterial stiffness index cfPWV in sedentary people was 26% higher than the age-matched senior athletes.[62] Additionally, sedentary men exhibited a more prominent age-related decline in endothelial function than their peers who exercised regularly.[208]

Physical exercise that lasts 12 weeks can effectively restore impaired endothelial-dependent vasodilation in both hypertensive patients and the normotensive elderly,[209] possibly attributed to the enhancement of NO release as well as the reduction of oxidative stress and inflammatory responses.[210,211] A longitudinal study showed that the age-related increase in baPWV was delayed in exercise-training people. After 10 years of follow-up, there was a 5.0% increase in baPWV among men who regularly exercised and a 13% increase in their inactive peers.[212] With aerobic exercise for 3 months, central artery elasticity was effectively restored in sedentary subjects in a cross-sectional study.[213] Notably, endurance exercise seems to have different effects on the structure of the carotid and peripheral arteries, therefore, producing debated results on whether endurance exercise can reduce the age-related increase in carotid IMT.[214–218] More likely, endurance training changes the local arterial shear stress of the femoral artery and has little effect on the carotid artery.

Nevertheless, in healthy older adults, a decrease of nearly 11% in IMT and 9% in femoral arterial lumen diameter were detected 3 months after aerobic exercise intervention.[218] Interestingly, it was found that racquet players had lower carotid IMT values than inactive peers. Their study suggested that more vigorous and intensive exercise is required to reduce carotid IMT.[219] In contrast to endurance training, chronic resistance training has negative effects on arterial elasticity.[220] The resistance-trained subjects showed a prominent age-dependent reduction in arterial elasticity compared with the sedentary-control subjects.[220]

Dietary Control

Diet habits influence vascular function profoundly. For example, the Mediterranean diet improves vascular function, while high-fat diets can acutely impair endothelial-dependent vasodilation.[221,222] Thus, dietary control provides a cost-effective way to prevent vascular aging.

Several studies reported that Mediterranean diet consumption significantly improved FMD in healthy older adults, obese individuals, and patients with metabolic syndrome.[223–225] It has been shown that the six-week low-fat diets (30% of total calories from fat) restored endothelial function in obese individuals, and increased FMD by 34%.[226,227] An eight-week of low-fat diet reduced cfPWV in hypercholesterolemic patients, and the decreased cfPWV was significantly correlated with the reduction of plasma CRP levels.[228]

A high-fiber diet was associated with a low risk of CCVDs,[229] decreased carotid IMT,[230] restored endothelial dysfunction in patients with metabolic syndrome,[231] and prevented endothelial dysfunction caused by high-fat meals.[232,233]

Excessive salt intake is another life habit that impairs vascular function.[234–237] The arterial elasticity in untreated hypertensive patients was significantly improved after 2 weeks of salt restriction,[238] and the age-dependent growth of cfPWV was effectively delayed during 2 years of salt restriction in normotensive people although the salt restriction did not decrease blood pressure, compared with the normal diet group.[239] These findings suggest that the beneficial effects of a low-salt diet do not depend solely on blood pressure reduction.

Caloric restriction is considered to be an effective nutritional intervention to delay vascular aging.[240,241] In hypertensive obese individuals, baseline forearm blood flow did not change after 2 weeks of a low-calorie diet (800 kcal/day), but endothelium-dependent vasodilation improved.[242] The study in overweight young adults also revealed a 10% weight loss and a 3.3% increase in FMD after 6 weeks of a very-low-calorie diet (580 kcal/day).[243] In a longitudinal study, the FMD

of obese diabetic patients increased from 5.64% to 10.16% after 8 weeks of caloric restriction (1000 kcal/day) and continued to increase to 12.46% over the next 44 weeks.[226] Another trial showed no difference in FMD changes between the caloric restriction group and the control group, however, PWV was decreased by 1.2m/s in the caloric restriction group after 3 months of a low-calorie diet (<1400 kcal/day).[244]

Intermittent fasting, time-restricted food intake, is another way to control energy intake.[245] Current knowledge about its effect on our blood vessels is very limited. In a comparative study, circulating markers of endothelial function (total nitrate, asymmetrical dimethylarginine, vascular cell adhesion molecule-1) were improved in patients with metabolic syndrome after 8 weeks of a 2-day fasting dietary schedule.[246] Furthermore, a recent animal study reported an increase in FMD in obese rats undergoing 6 weeks of intermittent fasting.[247] More studies are required to delineate the effects of intermittent fasting on vascular aging. It is important to understand that both, the strength and timing, present a large effect on the outcome, and may explain the conflicts which are not discussed here.[248–251] The interventions of vascular aging and their outcomes are outlined in Table 4.

Anti-Aging Therapy

The above strategies mainly focus on controlling risk factors of vascular aging to delay this process and have far-reaching significance. However, these measures alone seem to be insufficient in solving the problem. Currently, the most promising therapeutic approach in delaying vascular aging is anti-aging therapy, which relies on compounds that straightforwardly target molecular mechanisms underlying cellular senescence.

Senolytic is a kind of chemotherapeutics, which refers to the group of drugs that can selectively eliminate senescent cells. The common combination is dasatinib and quercetin. Recent studies have confirmed that senolytics can improve many age-related diseases and extend life span in aged mice.[252–254] Besides, senolytics can significantly reduce senescent cells in the medial layer of the aorta in the atherosclerotic model mice ($ApoE^{-/-}$) and improve the vasomotor response to NO.[255] Moreover, eliminating senescent cells can increase atherosclerotic plaque stability and prevent the development of atherosclerotic lesions.[256]

Table 4 Interventions for Vascular Aging and the Beneficial Effects

Interventions	Influence on Aging-Related Vascular Indicators	Ref
Anti-hypertensive agents		
ACEI	FMD↑, cfPWV↓	[132,135]
CCB	cfPWV↓	[135,139]
β-blocker	cfPWV↓, AIx↓	[135,147]
Diuretics	cfPWV↓	[135]
ARB	cfPWV↓, AIx↓	[144,145]
AdRB	cfPWV↓	[139]
Diabetes treatment agents		
Metformin	FMD↑, carotid IMT↓, AIx↓, cfPWV↓	[160,162,163]
Thiazolidinediones	Carotid IMT↓	[164–166]
Sodium-glucose co-transporter-2 inhibitor	FMD↑, cfPWV↓	[162,169]
Lipid-lowering agents		
Statins	Aortic root diameter↓, carotid IMT↓	[195,196,206]
Healthy lifestyles		
Physical exercise	FMD↑, baPWV↓, femoral arterial diameter↓, carotid IMT↓	[209,212,213,218,219]
Dietary control	FMD↑, cfPWV↓, carotid IMT↓	[223–225,228,230–233,239,242–244,247]

Abbreviations: AIx↓, AIx value decrease; Aortic root diameter↓, aortic root diameter decrease; BaPWV↓, baPWV value decrease; Carotid IMT↓, carotid IMT decrease; CfPWV↓, cfPWV value decrease; Femoral arterial diameter↓, Femoral arterial diameter decrease; FMD↑, FMD value increase.

Metformin is not only a commonly used drug for diabetes, it also has direct cardiovascular protective effects.[257] Age-related vascular indicators such as IMT, FMD, AIx and PWV were improved in diabetic patients with metformin.[160,162,163] Furthermore, studies demonstrated that metformin can delay cellular senescence.[252] The underlying mechanisms are complex and not fully understood.[258] There was a mass of papers investigated the anti-aging actions of metformin with data obtained from various species include *C. elegans, Drosophila melanogaster*, rodents and humans. Nonetheless, their conclusions are controversial, with some reviews being supportive of the anti-aging effect of metformin,[259–261] whereas others hold different opinions.[257,262–264]

Rapamycin is mTOR inhibitor. It has been reported to increase life span in many species,[265–267] and also it can inhibit the senescence-associated secretory phenotype of senescent cells.[268] Besides, plenty of evidences demonstrate that rapamycin has cardiovascular protective benefits. In old mice, after treatment of rapamycin, the endothelial-dependent dilation and NO bioavailability were largely improved, potentially due to its action in mediating redox balance or inflammation in advanced age.[269] In addition, structural changes of aged vasculature may be ameliorated, contributing to attenuated age-related vascular stiffening.[269] More importantly, these cardiovascular protective benefits were also confirmed in human. Studies have reported that those who received rapamycin therapy after kidney transplantation have significantly greater FMD, PWV and AIx.[270,271]

Nicotinamide adenine dinucleotide (NAD^+) is a coenzyme that catalyzes cell metabolism and can enhance Sirtuins 1 activation.[272] Its concentration is decreased in senescent cells. Many studies have demonstrated that supplementation of NAD+ precursor can retard cellular senescence and prolong lifespan.[273,274] Moreover, supplying NAD+ to old mice can reverse their age-related endothelial dysfunction and arterial stiffness.[275] Nevertheless, when translated to humans, only vascular elasticity, no endothelial function, was found to improve after providing people with NAD+ precursor for 6 weeks.[276] These evidences proved that Sirtuins 1 activation may be effective in ameliorating vascular aging.

Anti-aging therapy has now become a promising weapon in age-related diseases. However, there is still a long way to go "from bench to bedside".

Summary and Discussion

Blood vessels change their structures, functions, and compliance along the aging process. These changes can be detected and visualized to assess the degree of vascular aging directly; 1) Structure: both arterial wall thickness and lumen diameter are increased. 2) Function: the endothelium-dependent vasodilation induced by acetylcholine or reactive hyperemia becomes desensitized. 3) The vascular compliance: stiffness, which is measured by PWV or AIx, is increased. In addition to these direct measurements, the laboratory tests can provide many other indirect biomarkers or indicators for vascular aging, for example, endothelial progenitor cells, lymphocytic telomere, advanced glycation end-products, and C-reactive protein, as these biomarkers are well correlated with direct measurements.

However, it should be noted that these parameters reflect different information about arterial properties and may not be interchangeable even in the same category. For example, PWV and AIx are not fully consistent at all ages. Importantly, most of these parameters are influenced by not only age but also other factors, such as health status, gender, and lifestyle, and not all parameters are linearly correlated with age, while, some of them are only altered in the elderly population. Therefore, it is essential to measure multiple parameters to get a broader assessment of vascular aging.

Many diseases, particularly cardiovascular and metabolic diseases including their risk factors, significantly affect vascular aging. Thus, treating these diseases and avoiding the relevant risk factors prove to be effective in the prevention of vascular aging. Notably, only a few approaches can improve all parameters for vascular aging, since the outcome of the intervention is affected by many factors, such as strength, frequency, and age. This again points to the importance of measuring multiple parameters to evaluate the results of applied approaches to evaluate their abilities in preventing vascular aging.

It is worthy of being mentioned that there also exist controversies in both vascular phenotypic alterations and the outcomes of interventions. For example, whether aortic root dilation is a reasonable marker for vascular aging, as it is influenced by many factors, including body surface area, and how the listed indirect laboratory tests reflect vascular aging specifically. We also leave some questions that need more investigations to clarify. For instance, which clinical assessment(s) cover(s) more vascular changes with ages and can be used as a representative indicator(s) to quantify

vascular aging and which intervention gives best outcome, and so on. Answers to these questions not only provide an update in knowledge but also make a step forward to clinical translation in vascular aging.

In summary, vascular aging is a multi-dimensional process that requires a comprehensive set of parameters to be measured in clinical practices and it can be prevented to maintain healthy vasculature by avoiding modifiable risk factors and adhering to a healthy lifestyle.

Abbreviations

ACERI, angiotensin-converting enzyme inhibitors; AdRB, aldosterone receptor blockers; AGEs, advanced glycation end-products; ARB, angiotensin receptor blockers; AIx, augmentation index; baPWV, brachial-ankle PWV; BSA, body surface areas; CCB, calcium channel blockers; CCVDs, cardio-cerebral vascular diseases; cfPWV, carotid-femoral PWV; CRP, C-reactive protein; EPC, endothelial progenitor cell; FMD, flow-mediated dilation; IMT, intimal-medial thickness; LTL, leukocyte telomere lengths; NAD^+, nicotinamide adenine dinucleotide; NO, nitric oxide; PWV, pulse wave velocity; RAGE, receptors for AGE.

Ethic Statements

The processes that we achieved vascular tissues from patients conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of The Second Affiliated Hospital of Nanchang University.

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Disclosure

The authors declare no conflicts of interest in this work.

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