Aging Pathobiology and Therapeutics 2026; 8(3): 293-308 ***293***
DOI: 10.31491/APT.2026.09.234

REVIEW

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Pathogenesis and pathobiology of imaging vascular biomarkers during the aging process: a narrative review

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This article belongs to the Special Issue: Ever evolving hallmarks of aging

Abstract

The vasculature is a highly complex organ system capable of sensing alterations in its surroundings, promptly transducing signals to vascular and surrounding tissue cells, and synthesizing local mediators that induce both acute and chronic functional and structural adaptive responses. Vascular aging (VA) results from the combined effects of congenital and acquired risk factors and their interactions, and is a natural and inevitable contributor to age-related cardiovascular (CV) diseases. Atherosclerosis, arterial hypertension, and other CV diseases progressively lead to vascular dysfunction through multiple consecutive and interconnected pathological processes, including oxidative stress with reactive oxygen species formation, endothelial dysfunction, mitochondrial dysfunction, systemic inflammation, and autophagy. As molecular and signal transduction mechanisms become increasingly central to understanding vascular disease pathology—and as the interplay between basic science and clinical experience often yields counterintuitive findings—this narrative review summarizes the pathological changes of VA, tracing the process from the cellular level to clinically manifest vascular disorders, and describes in detail the most important imaging markers of the aging process. Furthermore, the review examines the essential mechanisms of vascular aging–related dysfunction from a fresh mechanistic perspective, aiming to inform and optimize the development of novel treatment strategies for patients with age-related CV diseases.

Keywords: Vascular aging, endothelial dysfunction, imaging vascular biomarkers, arterial stiffness, vascular remodeling, inflammation, oxidative stress

Introduction

Despite extraordinary advances in cardiovascular (CV) medicine during the 20th century, CV diseases remain by far the most frequent cause of global death and serious morbidity, particularly in industrialized countries. However, there is substantial cause for realistic optimism: research on CV disease and therapy has never been more active and productive, and it has brought the field to the threshold of major practical advances. The most important CV research is based predominantly on advances in basic science—molecular medicine. For more than half a century, medical physiology, often called the queen of the biomedical sciences and described as the logic of life, has provided the principal theoretical underpinnings for clinical developments in CV medicine. More recently, the application of cellular and molecular biology to CV clinical medicine has become increasingly evident in everyday clinical practice.

Biomarkers of aging can be characterized as "quantitative parameters of an organism that, either alone or in a composite, predicts biological age and ideally its changes in response to age-related interventions" [1, 2]. Aging biomarkers are important tools to comprehend and monitor the aging process. The so-called evolutionary theory of aging has laid the foundations for a more comprehensive perception and understanding of the complex aging process through a multilayered mechanism of action [3, 4]. Aging is, broadly speaking, characterized by a progressive, unstoppable loss of systemic physiological integrity, gradually inducing systemic dysfunction, increased proclivity to all-cause mortality, and all acquired major

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Received: 08 July 2026 / Revised: 25 August 2026
Accepted:22 September 2026/Published:30 September 2026

human chronic diseases, including both benign and malignant neoplasms (evolution from six to ten hallmarks of cancer), diabetes mellitus, a broad spectrum of CV disorders, chronic inflammatory systemic diseases, and, finally, neurodegenerative diseases (as the brain is the most sensitive organ to reductions in blood oxygen levels) [3, 5-10]. Multiple experimental attempts (and numerous ongoing investigations today) have been made to identify the root causes of gerontogenesis. Since 2013 and the proposed mechanism of aging by Lopez-Otin and his coworkers, many fundamental "hallmarks" of the maturation process have been detected, encompassing systemic inflammation, mitochondrial dysfunction, telomere attrition, loss of protein homeostasis, cellular senescence, stem cell exhaustion, and (epi-)genomic modifications [3, 6, 7, 9].

Dr. Thomas Sydenham, in the literature better known as "The English Hippocrates", once announced, "A man is as old as his arteries." This short but profoundly impactful declaration continues to resonate in the scientific community and among practicing clinicians more than four centuries since its initial use. Aging is a key risk factor for most known CV diseases, including atherosclerosis, arteriosclerosis, and arteriolosclerosis [8-10]. Nevertheless, vascular pathophysiological molecular processes occur across many diseases and states and are not an inevitable feature of maturation alone [10-12]. Multicenter, large-sample cohort studies with detailed arterial phenotyping, combined with demographic, laboratory, and clinical data, are crucial for an in-depth understanding of the factors related to resilience or predisposition/susceptibility in human age-related vascular pathophysiology [8-12]. The most important submolecular and cellular actions constituting the basis of aging vascular adjustments encompass (among others) aberrant cellular signal transduction and oxidative stress with its end-products [9, 10]. Genetic studies reveal intricate mechanisms that closely influence the grade of vascular aging (VA); even centenarian studies emphasize the impact of genetics on aging, particularly in the extremely old [10-12].

Aging is well recognized as an important risk factor for a plethora of diseases. The main focus of this review will be to define the most important vascular imaging markers of the physiological aging process (normal VA) by sampling representative articles from the previously published literature. Imaging markers generally provide critical insights in evaluating disease risk, guiding prognosis, anticipating drug responses, and discovering and developing new therapies, thereby helping improve precision and effectiveness in healthcare. Based on published data, the most important documented direct and indirect VA imaging markers are: endothelial dysfunction, arterial stiffness (AS), carotid intima-media thickness (CIMT), arterial tortuosity (AT), fat attenuation index (FAI), and left ventricular mass index (LVMI). AS seems to be the most important among them, due to its particularly high correlation with VA changes. From the clinical radiologists' point of view, the correlation of all VA imaging markers together with anamnesis, clinical physical examinations, and biochemical-laboratory examinations is optimal for a more comprehensive picture of this complex process and its proper staging and therapeutic decision.

Moreover, the integration of radiological with other parameters made so-called scoring systems (*i.e.*, SYNTAX I score, SYNTAX II score, Agatston coronary artery calcium score, carotid plaque score, coronary artery disease-reporting and data system severity [CAD-RADS] score, Gensini score, *etc.*), considered by some as one of the top discoveries in CV medicine, which have the highest diagnostic, prognostic, and predictive power (both short- and long-term), and are of particular value for clinical radiologists in everyday decision making. Additionally, the near future could bring official recognition of a new VA imaging marker and scoring systems, which could show an even more precise correlation with the molecular aging processes.

Molecular and clinical features and pathophysiology of VA

Endothelial function and dysfunction

Although AS is generally considered the most sensitive and earliest VA marker, the first listed is the endothelium and its function, because it is well proven that changes in endothelial function are closely connected with other important vascular morpho-functional parameters (*i.e.*, AS, CIMT, vascular plaque thickness, LVMI, AT, *etc.*), and that it precedes the other pathophysiological cascade changes in the CV system.

The endothelium represents histologically a continual and physiologically uninterrupted single-cell luminal layer that lines the inner space of the CV system, separating the intimal layer from the media by a basal lamina. The vascular tonus, therefore, represents a quite dynamic physiological entity influenced by a variable degree combination of secreted vasoconstrictors, vasodilators, and blood flow circulating substances, and therefore, vascular tonus alteration, in other words, is affected mainly through a combination of central and local regulation mechanisms [13, 14]. Compensating adjustments to vascular tone (short-term acute adjustments) or structure (long-term chronic adjustments) occur, with repercussions for the complete CV system and the organism as a total undivided unit.

The vascular endothelium by producing several vital chemical substances (*i.e.*, very important gaseous molecular messenger and important vasodilator agent nitric oxide (NO), potent vasoconstrictors like endothelin-1 and angiotensin II, prostacyclin, acetylcholine, adenosine triphosphate, bradykinin, thrombin, endothelium-derived hyperpolarizing factor—still awaiting more complete identification, *etc.*) has so many important functions for the whole human CV system, among them one of the crucial roles is listed here in the next order: plays a critical role in the regulation of both angiogenesis and vasculogenesis, has a key role in blood flow optimization and modulation, vascular tone regulation, CV homeostasis (through smooth muscle function regulation, platelet aggregation modulation, disaggregation of aggregating platelets, modulation

of white cell/leukocyte adhesion and transendothelial migration regulation, inhibition of neointimal hyperplasia, *etc*.), metabolic, immunological and inflammatory state regulation, has an antioxidizing effect, as well as providing anatomical vessel wall barrier functions (serving as a barrier for the exchange of fluid, electrolytes, macromolecules, and cells between the intra- and extravascular space, *etc.*) [13-15]. Thus, the endothelial lining is, so to speak, the maestro of the vasculature, playing a key role in the regulation of both vascular wall integrity and hemostasis. Multiple previous published studies have therefore suggested that aging directly contributes to endothelial dysfunction, primarily by increasing oxidative stress through the generation of reactive oxygen species (ROS) via a bound membrane complex called nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, increased arginase activity, and, to a lesser extent, reduced tetrahydrobiopterin bioavailability, which promotes nitric oxide synthase (NOS) uncoupling and further superoxide production [16, 17].

ROS are considered highly reactive biochemical species that are created both physiologically as a natural derivative of complex oxygen metabolism reactions, as well as pathologically in the course of environmental and oxidative stress. More importantly, increased ROS formation and inflammation, combined with decreased NO production and plasmatic bioavailability, are the principal pathomechanisms of endothelial dysfunction (superoxide anion is the primary ROS in the endothelium). This so-called age-related endothelial dysfunction is also influenced by people's gender. It has already been demonstrated to occur approximately a whole decade (8–12 years) later in women compared to men [18]. Presumably, women's hormones, particularly estrogen, and their vasculoprotective role, are the main reasons for this difference.

Moreover, MYBL1 (a key member of the MYB family of transcription factors), which already has a proven role in oncology, is presumably also very actively involved in CV diseases, including age-related CV pathology. Evidence suggests that MYBL1 is low-expressed in atherosclerotic plaque tissues, and it can participate in the disease progression by regulating the proliferation and migration of human umbilical vein endothelial cells [19].

The synthesis and release of the endothelium-derived relaxing factor is probably the most significant role performed by the endothelium in regulating vascular tone. The year 1980 will in vascular medicine and physiology always be remembered. Furchgott and Zawadzki conducted experiments on a rabbit's isolated aorta with a well-preserved endothelium, indicating that acetylcholine causes vasodilation, while in the case of a damaged endothelium, it causes, in contrast, vasoconstriction [20]. Since then, the concept of so-called endothelium-dependent relaxation has been worldwide introduced, and over the following years, it has been established that the diffusible half-life substance is biochemically identical to NO [21, 22]. Interest in the NO biology and chemistry formation was germinated by previously mentioned findings by Furchgott and

Table 1. Molecular mechanisms, pathological effects, and corresponding imaging markers of vascular aging.

VA imaging marker	Molecular pathway	Primary pathological effect	Most relevant imaging marker	Level of supporting evidence
Endothelial dysfunction	Increased ROS formation through NADPH oxidase, increased arginase activity, and reduced NOS activity	Decreased NO synthesis and activity	FMD	High
Arterial stiffness	Numerous pro-inflammatory cytokines and adhesion molecules (*i.e.*, TNF-α, MMPs, MFG-E8, VCAM-1, ICAM-1, IL-6, IL-18, IL-1β, MCP-1, IL-13, IL-10, IL-4, *etc*.) intervene in this process	VSMCs switch to secretory phenotype with alteration of the ECM composition—increasing collagen component and collagen-to-elastin ratio, and MMP synthesis with increased proteolytic activity	PWV	High
CIMT and carotid plaque thickness	Aggregation of extracellular and intracellular lipids, monocyte and macrophage infiltration, formation of foam cells, VSMC proliferation, and aggregation of various connective tissue proteins	Increased thickening of the intima-media layer with carotid plaque formation	Carotid duplex ultrasonography	High
Pro-inflammatory conditions	Activation of NF-κB and various pro-inflammatory signaling pathways, with increased oxidative stress and ROS formation	Perivascular and vascular inflammation promoting atherosclerosis susceptibility	FAI	High
Arterial tortuosity	Genetics	Elastin fragmentation with increased collagen-to-elastin ratio	ATI	Medium
Left ventricular hypertrophy	Pressure and hemodynamic overload	Hypertrophy of the cardiomyocytes	LVMI	Medium

Notes: ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; NOS, nitric oxide synthase; NO, nitric oxide; TNF-α, tumor necrosis factor-alpha; MMPs, matrix metalloproteinases; MFG-E8, milk fat globule-EGF factor 8; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular cell adhesion molecule-1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; VSMCs, vascular smooth muscle cells; ECM, extracellular matrix; NF-κB, nuclear factor kappa-B; CIMT, carotid intima-media thickness; FMD, flow-mediated dilatation; PWV, pulse wave velocity; FAI, fat attenuation index; ATI, arterial tortuosity index; LVMI, left ventricular mass index.

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Zawadzki, and the explosion of this new field led to the discovery of a family of three different NOS, their respective prompt purification from different molecular sources, cloning, characterization, and finally designation as three different dimeric enzyme isoforms (neuronal nitric oxide synthase [nNOS], inducible NO synthase [iNOS], and endothelial nitric oxide synthase [eNOS]). The principal task of the endothelium in balancing the morphological blood vessel structure results from the endothelium responding to two simultaneous and mutually dependent influences: the hemodynamic force of pulsatile blood flow and humoral agents of circulating liquid [14, 22].

The most illustrative practical example of the effects of NO on the endothelium-smooth muscle complex is the transitory increase in vessel diameter during reactive hyperemia, where ischemia is immediately followed by the maximum velocity of laminar blood flow (endothelium-dependent vasodilatation or flow-mediated dilatation [FMD]). Although extensively studied for almost half a century, the endothelium has remained an ever-current research topic.

Based on the results of numerous meta-analyses, the most important risk factors affecting the endothelial function are as follows: the process of aging, cigarette smoking (active or passive), high lipoprotein fraction plasmatic levels (low-density lipoprotein, very low-density lipoprotein, lipoprotein-α) mainly through so-called oxidized low-density lipoprotein-induced endothelial injury, hyperhomocysteinemia, diabetes mellitus, and low birth weight—the interaction of several of these factors exerting the most significant influence [23]. Aging is a process related to multiple simultaneous CV structure and function alterations, with normal aging being clearly distinguished in literature from the accelerated one [14, 23, 24]. Both processes have the same core and are based on the increase in blood vessel thickness and AS. Yet, in normal aging, this process is gradual and related to left chamber mass growth and higher values of systolic blood pressure, while in accelerated aging, it is related to significant concomitant adjustments in endothelial and vascular smooth muscle cells (VSMC), and followed by a consecutive fast development of early atherosclerotic lesions [24].

It is believed that females, particularly in their premenopausal period, are better protected from vascular diseases in general than males. Further in-depth understanding of how maturation causes endothelial dysfunction is crucial. Most importantly, it is known that NO and AS expressed via pulse wave velocity (PWV) have an inverse relationship; decreased NO production and bioavailability, which increase AS and elevate PWV values. Table 1 is summarizing what is mentioned in the previous paragraphs regarding the complex VA pathophysiological submolecular processes, and the most important VA imaging markers, their molecular pathways and known mutual interrelations.

AS

AS has various and numerous definitions and practical meanings; however, one of the most accurate is that it measures the arterial wall's resistance to the vasodilation process—sudden arterial luminal and inter-adventitial diameter and volume increase [25]. AS is also described by both structural (for example, tunica media calcification, subtle morphological and histological VSMC modifications, and finally fibrosis and many fibrotic changes) and functional (*i.e.*, global elevation in pulse pressure, loss of Windkessel function, and gradual build out of isolated systolic hypertension and finally global arterial hypertension) vascular deterioration that consequently in time produces microvascular dysfunction and multiple end-organ damage and dysfunction (*e.g.*, heart failure, vascular dementia, Alzheimer's disease, leukoaraiosis, cognitive decline, hypertensive retinopathy, and chronic kidney disease) [25, 26]. In line with the previous, it is widely regarded by most authors, clinicians, academics, and scientists worldwide as one of the key features and most important hallmarks and parameters of the VA process [25]. It is also regarded as an early VA imaging marker.

In routine clinical practice, it is most commonly measured by the parameter PWV, often described as an integrated index of vascular function, in the largest and highest diameter elastic arteries, such as the aorta (most commonly the thoracic and abdominal aorta), carotid arteries (common carotid artery [CCA], internal carotid artery [ICA], and external carotid artery [ECA]), and common femoral arteries, and sometimes even their distal offshoot branches.

While increased AS index values can occur in various and multiple disease conditions and states, particularly including today's most prevalent CV diseases like arterial hypertension and type 2 diabetes mellitus, it is believed by most authors, clinicians, and scientists to have the strongest and most important correlates and association with the physiological aging process [26].

The physiological aging process has been documented to increase AS through its effects on the endothelium–smooth-muscle complex—namely, by affecting both the endothelial cell layer and VSMCs (with the latter switching to a secretory phenotype) at the submolecular level, and in the chronic phase by irreversibly altering the extracellular matrix (ECM) composition, increasing the collagen component and the collagen-to-elastin ratio, all of which are essential factors for maintaining optimal vascular compliance [27-29]. From the earliest embryological development through gerontogenesis, the vascular ECM undergoes complex biochemical, biophysical, and biomechanical changes in response to diverse environmental signals and cues, and dictates precise regulatory control over vessel morphological development and remodeling throughout the mechanical microenvironment of the vasculature [28, 29].

It is believed that the aging process gives rise to vascular stiffening by stimulating matrix metalloproteinase (MMP) creation and secretion from VSMCs, with VSMCs switching to secretory phenotype and also MMP proteolytic destructive activation (pivotal molecular basis for the AS pathogenesis) [30, 31]. Score of multiple pro-inflammatory cytokines and adhesion molecules (*i.e.*, TNF-α, MMPs,

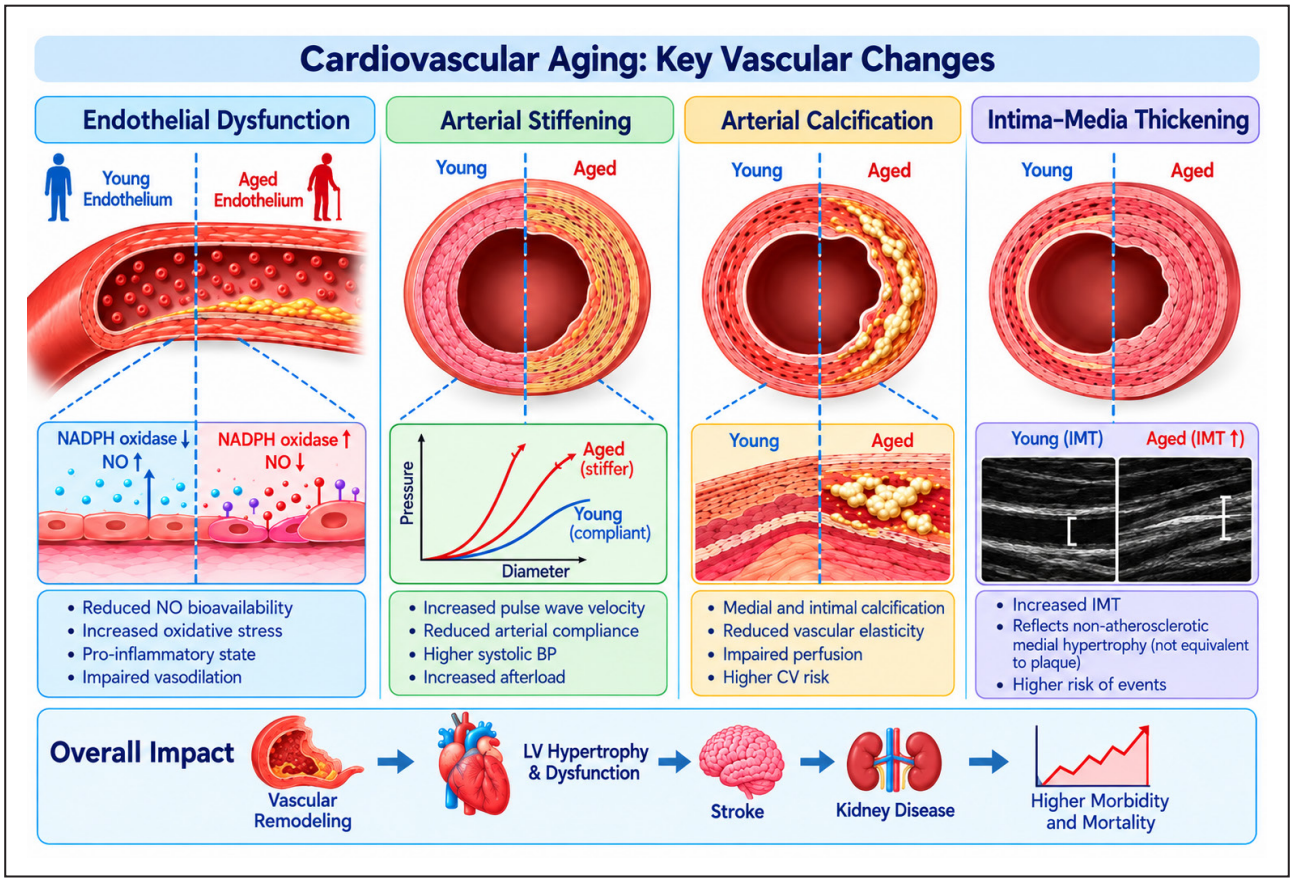


Figure 1. Schematic overview of key vascular changes in cardiovascular aging. Each panel contrasts young and aged vessels: endothelial dysfunction (reduced nitric oxide bioavailability and impaired vasodilation), arterial stiffening (increased pulse wave velocity, reduced compliance), arterial calcification, and intima-media thickening (ultrasonographic appearance shown as an illustrative example). The lower panel summarizes the overall clinical impact: vascular remodeling contributes to left ventricular hypertrophy and dysfunction, stroke, and kidney disease, resulting in higher cardiovascular morbidity and mortality. Illustrative diagram; not to scale.

MFG-E8, VCAM-1, ICAM-1, IL-6, IL-18, IL-1β, MCP-1, IL-13, IL-10, IL-4, *etc*.) intervene in this process. Namely, multiple MMPs and inflammatory cytokines act together and form a cornerstone of vascular morphological remodeling pathophysiological cascade through destructive proteolytic processes, such as increased actin network, collagenolysis and elastolysis and fragmentation, adhesion to fibronectin, breakdown of collagen fibers by enzymes (appearing as altered—often eosinophilic or basophilic material with inflammatory cells in tissue section) as well as repeated collagen synthesis with increased apoptosis and autophagy [32].

Furthermore, these molecular alterations of elastin fragmentation are believed to be a significant contributor to the well-documented histological changes inside large aging arteries, specifically the increase in collagen tissue fibers and the collagen-to-elastin ratio [33]. The molecular basis of this ratio change is presumed to lie in altered collagen and elastin cross-linking: desmosine and isodesmosine (elastin cross-links) decrease with age, whereas pyridinoline (a collagen cross-link) increases [34]. The combined effects of repeated MMP secretion, vascular proteolysis and fragmentation, cross-link deterioration, and increased mechanical and oxidative stress contribute to elastic lamellae rupture and fragmentation—one of the driving forces behind aging-related AS [35]. Parallel with these processes, residual mast cells and inflammatory cells migrate from the intima to the adventitia in the most advanced atherosclerotic lesions. Additionally, the expansion of collagen fibers and the collagen-to-elastin ratio in senescence has a major vascular impact: together they reduce arterial elasticity and contractility; the gradually enlarging systolic ejection pulsatile force from the left ventricle is transferred onto collagen fibers, which are significantly stiffer (by a factor of 100 to 1000) than elastin fibers, leading to repeated fracture of the internal and external elastic lamellae, intensified rigidity, and, over time, consequential left ventricular (LV) hypertrophy (a circulus vitiosus of ventricular-vascular remodeling) [36].

Vascular stiffening is one of the initial signs of adverse structural and functional alterations (predominantly structural) within the vascular wall itself. Arteries also stiffen in other conditions such as arterial hypertension, diabetes mellitus, and chronic renal disease [37]. Widely considered as a quite authentic vascular biomarker, increased AS is one of the most important risk factors in both CV mortality and morbidity [38]. AS is an independent strong predictor (both diagnostic and prognostic) of coronary artery disease (CAD) and stroke in otherwise healthy subjects and an independent strong predictor of community-wide mortality and morbidity [39]. As previously written, PWV is quite a sensitive, reliable, and easy-to-reproduce AS in-

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dex in everyday clinical settings [40]. It has also emerged and is widely accepted as a proxy of VA, capturing the vascular continuum from early/accelerated to healthy VA [41]. Higher PWV values, therefore, practically translate to many functional shortcomings, unnecessary and supernumerary CV harm, and major undesirable future vascular events [38].

While diverse factors are involved in the aging of large arteries (some of them being written in the previous paragraphs), their strict interaction and reciprocity, and underlying action mechanisms remain a complex and highly active field of study. AS is strongly and significantly interconnected with higher arterial blood pressure levels (both systolic and diastolic values) and further involves the interplay between blood pressure and structural (*i.e.*, central arterial remodeling) vascular changes [38, 40]. The autonomic nervous system, through the sympathetic and parasympathetic nervous systems, and truncal obesity/adiposity represents an additional contributor to accelerated/pathological VA [38, 42]. Along with the previously mentioned determinants, physical exercise is also important for vascular senescence: the more physical activity, the lower the PWV. The main mechanisms linking regular physical activity to VA are arguably decreased systemic blood pressure and obesity/adiposity, combined with modulation of autonomic nervous system action [43, 44].

Figure 1 summarizes the complex VA pathophysiological submolecular processes described in the previous paragraphs. It is a diagrammatic representation of the CV aging process with highlighted key pathophysiological changes, articulating the temporal and causal progression from initial endothelial dysfunction to AS, structural remodeling, and ultimately target-organ damage; it highlights the role of chronic inflammation as a pervasive driver throughout this cascade, indicates the corresponding imaging tools for each stage, and cross-references the mechanistic details summarized in Table 1.

Intimal-media thickening and carotid plaque thickness

Atherosclerosis is the most common form of arteriosclerosis, a condition that encompasses all vascular diseases characterized by the thickening and hardening of the arterial wall. Atherosclerosis lies at the core of the most frequent diseases of today, such as heart and brain infarction. Although it is classified as a systemic disorder, atherosclerosis occurs first at predilection sites, primarily in the intima of elastic arteries (the abdominal aorta, the carotid and iliac arteries), and some large and medium-sized muscular arteries (the coronary, popliteal, and cerebral arteries), and it most often causes ischemic lesions of target organs [45]. It is marked by the aggregation of extracellular and intracellular lipids, monocyte and macrophage infiltration, the formation of foam cells, VSMC proliferation, and the aggregation of various connective tissue proteins [46]. Once described as a degenerative disease, atherosclerosis is now regarded in vascular biology as a chronic inflammatory disease—an intimal response to endothelial damage involving humoral and cellular immune reactions. The present-day 'response to damage' hypothesis, first anticipated by Anitschkov and later formulated by Ross. This hypothesis integrates the hypothesis of Rokitansky, who believed that an atheroma develops from the resorption and healing of a thrombus, and the hypothesis of lipid accumulation by Virchow, who regarded atherosclerosis as a proliferative disease [45, 46].

The lamina elastica externa is the border between the media and adventitia, and it is rich in the nutritional vascular system. Change in blood vessel structure during atherogenesis is not only one of the key changes but the most important modification [47].

The ultrasound examination of carotid arteries (precerebral arteries) with the measurement of the CIMT serves for monitoring the progress of asymptomatic atherosclerosis. The increase in CIMT is of importance for predicting the progress of atherosclerosis, coronary heart disease (CHD), and stroke [48]. The values of CIMT are also used as indicators of the VA process, which is a replacement for the chronological aging process, to improve the prediction of the potential risk of CHD by measuring the current atherosclerotic burden [49]. The 2008 American Society of Echocardiography (ASE) consensus statement on CIMT and the Mannheim CIMT Consensus defined CIMT as the combined thickness of the intima and media of the far wall of the carotid artery. The carotid plaque was defined as the focal thickness of the arterial wall that is at least 50% greater than the thickness of the surrounding wall, or a focal region where CIMT > 1.5 mm [50-52].

Standard carotid duplex ultrasonography is used to detect occlusive carotid plaque (advanced atherosclerosis), to measure CIMT and arterial wall thickness (pre-atherosclerosis), and to identify non-occlusive plaque (subclinical atherosclerosis). The methodology of ultrasonographic determination of the intima-media thickness (IMT) was described by Roman *et al*. and by Pignoli *et al*. using histopathological standards [53, 54]. The wall of the CCA has a characteristic hyperechogenic-hypoechogenic-hyperechogenic pattern at the far wall, called the intima-media complex; the measurement of its thickness is called the IMT, with an average value of 0.7 mm, and is used in numerous standardized protocols as an indicator and prognostic parameter of atherosclerosis (progression or regression) [55].

An additional vascular imaging parameter—the cross-sectional area of the CCA (CSA)—can be calculated when the luminal area is subtracted from the adventitia area, with radius being the sum of the inner diastolic radius and IMT, according to the following pattern: π [IMT + (lumen diameter/2)]^2 − π [(lumen diameter/2)]^2 [56]. More precise measurements of CSA are done by planimetry. CSA is a novel measurement that might provide an additional morphological tool alongside CIMT in clinical practice, although the size of the examined artery plays an important role.

The so-called Framingham Offspring Study—a flagship article considered groundbreaking by many—first showed the incremental effect of carotid artery plaque for risk prediction: plaque had higher predictive value for CV events than CIMT, and only maximum CIMT (and the presence

of plaque) in the ICA significantly, albeit modestly, improved CV risk classification [57]. This landmark article predated and inspired many other similar topic articles that further investigated the prognostic implications of both CIMT and carotid plaque thickness. Some data and articles point to the sex difference in the VA process (*i.e.*, mostly slowing aging deterioration in female subjects), including CIMT as a parameter [58]. Building on this evidence, Figure 2 shows more precisely how specific initial molecular and submolecular changes translate into measurable imaging signals and clinical and pathophysiological consequences.

Pro-inflammatory conditions, pro-atherogenic conditions, and plaque instability

As previously written, systemic inflammation, and particularly vascular inflammation—often metaphorically described as another brick in the wall for diagnostics generally, has already been acknowledged as one of the leading atherogenic promoters, particularly in acute, complicated clinical scenarios [59]. This process can occur in practically every arterial vessel of varying diameters. Epicardial adipose tissue histologically consists of various amounts of adipocytes, preadipocytes, stromal-vascular cells, nerve cells, and immune cells, with the unique feature of sharing microcirculation and being in very close contact with the myocardium. In conditions like obesity, epicardial adipose tissue increases and has been identified as a metabolically active organ capable of releasing pro-inflammatory and pro-atherogenic molecules, including TNF-α, IL-1, IL-6, leptin, and angiotensinogen. Dysfunctional epicardial adipose tissue, on the other hand, releases hypoxia-inducible factor-1α (HIF-1α), which increases myocardial NADPH oxidase activity and ROS production.

Advances in image resolution and analysis have enabled indirect quantification of this process in the coronary arteries by detecting subtle inflammatory changes in the surrounding perivascular fat, as assessed by computed

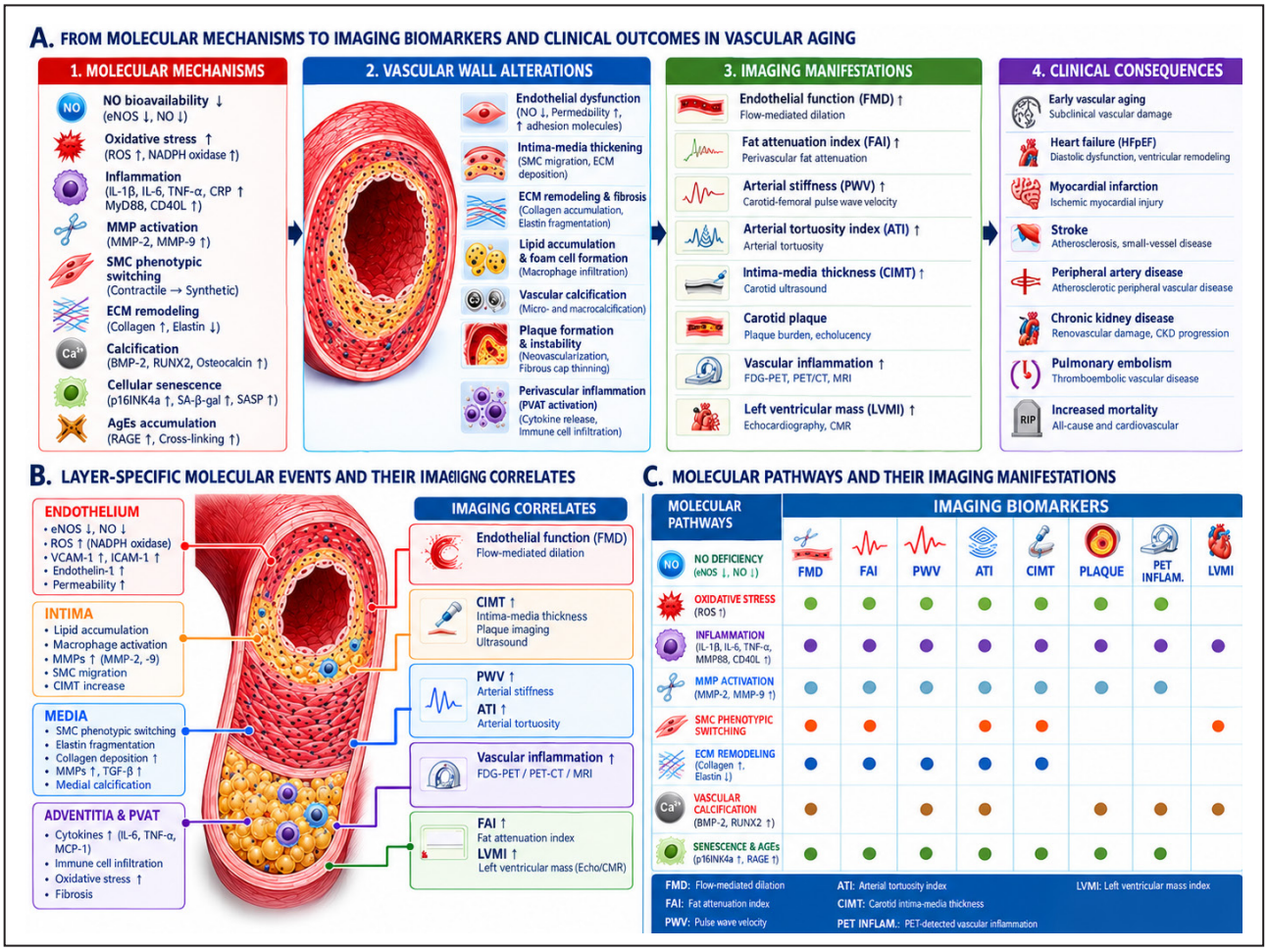


Figure 2. From molecular mechanisms to imaging biomarkers and clinical outcomes in vascular aging. (A) The pathophysiological cascade, shown in four stages from left to right: molecular mechanisms (reduced NO bioavailability, oxidative stress, inflammation, MMP activation, smooth muscle cell phenotypic switching, ECM remodeling, vascular calcification, cellular senescence, and advanced glycation end-product accumulation); vascular wall alterations (endothelial dysfunction, intima-media thickening, ECM remodeling and fibrosis, lipid accumulation and foam cell formation, vascular calcification, plaque formation and instability, and perivascular inflammation); the corresponding imaging manifestations (flow-mediated dilatation, fat attenuation index, pulse wave velocity, arterial tortuosity index, carotid intima-media thickness, carotid plaque, vascular inflammation on FDG-PET, and left ventricular mass index); and clinical consequences (early vascular aging, heart failure, myocardial infarction, stroke, peripheral artery disease, chronic kidney disease, pulmonary embolism, and increased mortality). **(B)** Layer-specific molecular events in the endothelium, intima, media, and adventitia/perivascular adipose tissue (PVAT), together with their imaging correlates. **(C)** Association matrix between molecular pathways (rows) and imaging biomarkers (columns); dots indicate the pathways associated with each imaging manifestation.

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tomography coronary angiography (CTCA) and the FAI [60]. This allows clinicians to gauge localized inflammation that drives morphological and functional vascular alterations, thereby increasing susceptibility to atherosclerosis and CAD. Although FAI is an indirect measurement of a very specific location, and inflammation is only to some degree connected to aging, this parameter deserves full attention from the scientific community, since damaged perivascular fat tissue is practically an endocrine organ that actively contributes to the vascular inflammation process. FAI thus functions as an early-warning "thermometer" of CV disease, able to detect risk before major obstructions are visible on standard CT. Regarding FAI reference values, higher (less negative) Hounsfield unit (HU) values signify increased inflammation and higher CV risk, with key thresholds such as FAI ≥ −70.1 HU for the right coronary artery (RCA); specific artery cut-offs (*e.g.*, left anterior descending ≥ −63.4 HU, left circumflex ≥ −61.6 HU) predict heart failure hospitalization, though values vary by artery (RCA is often preferred) and by technical factors.

Fat, primarily epicardial adipose tissue, is by academicians worldwide no longer perceived as a simple biological vasculature scaffold, but as a very important and potent secretory organ with powerful paracrine activity. In line with the previous, specific inflammatory infiltrations consisted of T-lymphocytes, mast cells, and macrophages ($CD3^+$, tryptase, $CD68^+$, respectively) combined with specific inflammatory mediators (*e.g.*, TNF-α, IL-6, MCP-1, and VCAM-1) were identified on mRNA (reverse transcriptase-PCR [RT-PCR]) and protein (ELISA) levels in epicardial fat, in the areas proximate to coronary lesions; whereas on the contrary, they were not detected practically at all in subcutaneous samples [60, 61].

Chronic, sterile, low-grade vascular inflammation, arguably a principal feature of aging, plays a pivotal role in promoting secretory phenotypic shifts in both VSMCs and endothelial cells, thereby facilitating and perpetuating a pro-inflammatory condition. More importantly, chronic low-grade vascular inflammation, often neglected clinically, may over the years lead to cumulative ("snowball") aging effects with multiorgan deterioration and functional decline. As documented, this multifaceted action begins with alterations in key signaling pathways—namely, activation of the renin-angiotensin-aldosterone system with endothelin-1 receptor A stimulation, creating a "vascular injury-inflammation feedback loop," as well as increased formation of advanced glycation end-products, particularly in subjects with type 2 diabetes mellitus—followed by activation of pro-inflammatory signaling pathways (including NF-κB and various pro-inflammatory cytokines: VCAM-1, IL-6, IL-18, IL-1β, MCP-1, IL-13, IL-10, and IL-4) and increased oxidative stress with ROS formation [61, 62].

This combined pro-atherogenic and pro-inflammatory milieu ultimately leads to vascular endothelial dysfunction through mitochondrial dysfunction, impaired cellular metabolism, increased oxidative stress with ROS formation, and enhanced apoptosis [63]. Increased ROS generation is presumably a key contributor to systemic microvascular damage and dysfunction, and finally to various age-associated forms of end-organ damage [64].

Additionally, it is documented that the co-stimulatory molecule CD40 ligand (CD40L) further boosts vascular inflammation by various mechanisms that include, in the first place, endothelial cell activation, consequent leukocyte migration into atherosclerotic plaques, the delivery of pro-inflammatory cytokines, and pro-thrombotic reactions [65]. Originally discovered on immune system cells (T and B cells), it is also expressed to a variable degree on the surface of other vascular cells (platelets, monocytes, endothelial cells, and VSMC) [66]. In ruptured atherosclerotic plaques, signaling pathways downstream of CD40L are upregulated, and the quantity of soluble CD40L (sCD40L) correlates with CV outcomes, suggesting that CD40L is very actively involved in human atherosclerotic plaque destabilization [65]. Consistently, CD40L deficiency or therapy with blocking anti-CD40L antibodies reduces atherosclerotic plaque size in an experimental mouse model [67]. Consistent with previous findings, it was also reported that CD40L communicates and cooperates with the leukocyte integrin Mac-1 and thereby plays an active role as a vascular adhesion factor in adequate leukocyte homing to atherosclerotic plaques and other inflammatory sites [68].

These age-determined vascular modifications not only contribute to a pro-atherogenic milieu but also govern the biochemical composition and vulnerability of the human atherosclerotic plaque throughout the entire disease process. Atherosclerotic plaque stability primarily relies upon two dominant factors—the thickness of the surface fibrous cap and the degree of inflammation—with thin-cap (< 65 μm) fibroatheroma being arguably one of the most common precursor lesions that precede plaque rupture [69]. Cap thickness and strength are of utmost importance, as plaque rupture—the most common cause of acute arterial thrombosis and potentially life-threatening myocardial infarction or stroke—drives preventive strategies.

Although coronary calcification is an imaging marker of coronary atheroma, dense calcification (> 400 HU) is usually associated with plaque stability on follow-up. Conversely, microcalcification (often referred to as spotty calcification) more commonly accompanies vulnerable plaques and is more closely associated with the likelihood of plaque rupture and major adverse CV events [69, 70]. Recent studies have suggested that microcalcification in the fibrous cap may act by increasing local tissue stress—depending on the proximity of one microcalcific locus to another and the orientation of the microcalcification relative to blood flow—resulting in markedly increased plaque instability [70]. Therefore, the destabilizing effects of calcification on human atherosclerotic plaques arise mostly from active inflammation and heightened biomechanical forces.

A recent experimental study by Gunnersen *et al*. showed that MyD88-dependent signaling promotes medial VSMC phenotypic modulation and the recruitment of cap VSMCs, linking inflammatory signaling to protec-

tive fibrous cap formation in murine atherosclerosis [71]. Accordingly, partial or complete deletion of *Myd88* in VSMCs in a mouse model of atherosclerosis mitigates the phenotypic modulation of medial VSMCs beneath lesions and diminishes their transition into fibrous cap VSMCs [72]. VSMC apoptosis in atherosclerotic plaques is one of the core changes that has been demonstrated to induce future plaque rupture predictors alteration (*i.e.*, collagen tissue and fibers fragmentation, rupture and breakdown, cap-thinning, and necrotic core growth—all of which alone, and particularly together, increase plaque vulnerability) [72].

More precisely, neutrophils accelerate plaque matrix degradation through the release of matrix metalloproteinase-9 (MMP-9), while the formation of neutrophil extracellular trap nets (NETs) can promote coronary microthrombosis. This persistent state promotes atherosclerosis development and directly triggers plaque rupture, thrombosis, and myocardial infarction (MI) [73, 74]. Aged VSMCs also exhibit some important cellular changes (*e.g.*, a significant decrease in proliferation rates and cell doubling time with polyploidization and upregulation of NADPH oxidase 4 (Nox4) in VSMCs), features which are comparable to those of VSMCs obtained from most advanced atherosclerotic plaques [73-75]. They are also more prone to start cellular senescence or irreversible growth arrest, which is mediated by increased angiotensin II molecular signaling pathways seen in the chronic inflammation pathway associated with the maturation process [75]. *In vitro* studies also indicate that plaque stability and progression are influenced by VSMC proliferation, as successful plaque repair relies on VSMC proliferation and ECM synthesis [76]. Therefore, the VSMC phenotype and its secretions are important determinants of plaque structure and vulnerability.

In clinical terms, plaque erosion accounts for approximately 30% to 35% of sudden coronary death cases, and thrombi are attributed to calcified nodules in 2% to 7% [77]. In many countries, even today, those numbers are unfortunately even less favorable, which should be considered even more devastating.

One more very important practical fact is that the CD40L and its soluble form (sCD40L), together with MyD88 and ROS formation, act as direct drivers of accelerated VA by promoting a chronic inflammatory state, therefore increasing major CV events. They also have various molecular activities, but when we are speaking regarding translation from subtle molecular changes into measurable imaging signals, they have the strongest connection with FAI, in terms that higher CD40L levels practically mean higher FAI, and finally higher vascular inflammation and most importantly more probability for major CV events. Because of those facts, therapeutic strategies aimed to block the cell-specific CD40/CD40L axis are the focus of preclinical/experimental investigations to decrease/stop age-related tissue destruction and vascular and systemic complications.

AT

The elastic properties of the aorta are essential to its normal functioning, and its elasticity and distensibility decline with aging [12, 13]. The gradual loss of aortic compliance probably accounts for the increase in pulse pressure commonly seen in the elderly. Histologically, the aging aortic wall shows progressive elastin fragmentation and destruction, accompanied by an increase in collagen fibers and thus an increased collagen-to-elastin ratio, generating the irreversible decline in aortic distensibility observed with age. Some preclinical animal data imply that impairment of vasa vasorum flow, primarily to the outer aortic wall, results in aortic stiffening with similar histological changes and may therefore be one root cause of these age-related degenerative adjustments [13, 14]. In animal models (primarily rats), decreased aortic distensibility (with final complete loss) directly affects LV mechanics, increasing LV systolic pressure, wall tension, and consequently end-diastolic pressure and volume. Furthermore, reduced aortic compliance with aging causes a variable (approximately 20–40%) adaptive increase in myocardial oxygen consumption to sustain a given stroke volume [14, 30]. It is therefore plausible that, over time, aging-related alterations in aortic compliance may induce clinically significant CV functional changes.

AT is another vascular geometric imaging marker, whose mechanobiological basis is not completely understood, generally described as the presence of variable degrees of vascular twisting with different resulting twist angles, most commonly in the aortic segments and mid-sized arteries. These vessels often twist as an embryological consequence of certain genetic diseases (*i.e.*, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, *etc.*) or acquired conditions [78].

One of the plausible causes that often operates during physiological aging is the slow, gradual abnormal lengthening of the arteries, due to histological composition differences, within a fixed or narrowed anatomical region (*i.e.*, the abdomen, thorax, *etc.*), which decreases the axial stress along the vessel and gradually leads to forced, variously shaped bending (*e.g.*, an S-shaped or similar geometric form) [78]. Other important influential elements and root molecular histological causes involve the non-physiological and abnormal allocation and aberrations in elastic fibers, as well as distortions of collagen alignment and turnover, predominantly in the medial layer of the arterial wall (tunica media), resulting in a gradually increased collagen-to-elastin ratio [12-14, 30]. These determinants stimulate abnormal and increased vessel AS, which subsequently leads to progressive and irreversible deterioration of structural stability [79]. What is more, the AT could appear concomitantly in or following an aneurysmatic segment, appearing for an additional interventional/surgical risk, in terms of vessel rupture [80].

Arterial tortuosity syndrome (ATS) is a recognized genetic and clinical entity (pathogenic variants in *SLC2A10* identified by ATS molecular genetic testing), characterized by CV findings—most commonly widespread elongation and tortuosity of the aorta and mid-sized arteries, concomitantly with focal stenosis of multiple segments of the pulmonary arteries and/or aorta—together with fea-

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tures of a generalized connective tissue disorder (soft or doughy hyperextensible skin, joint hypermobility and hyperelasticity, inguinal hernia, and diaphragmatic hernias) and skeletal changes (*i.e.*, pectus excavatum or carinatum, arachnodactyly, scoliosis, knee/elbow and other joint contractures, and camptodactyly) [80, 81]. CV complications are therefore the leading cause of morbidity and mortality in ATS. Patients are at risk of aneurysm formation and dissection at virtually any age, from the aortic root to the most distal arterial branches, as well as of acute and subacute ischemic events in the cerebrovascular circulation (causing ischemic or hemorrhagic stroke) and in the abdominal arteries (causing infarction of multiple abdominal organs).

In the past decades, AT has drawn much attention from the academician community and continuous effort has been put into improving the AT diagnosis, evaluation, and measurement, because AT is another very useful indicator of vascular fragility or underlying arteriopathies and other different pathologies, and different imaging techniques (*i.e.*, computed tomography angiography and magnetic resonance angiography) have become robust tools to examine the shape and condition of the aorta and its major offshoot vessels [82, 83]. Indeed, the arterial tortuosity index (ATI) has been identified as a potential vascular imaging marker of adverse long-term CV outcomes [83]. In an analytical study by Daniel Benítez Gracia, ATI was defined as the difference between the geodesic distance (the total measured length of the aortic track) and the Euclidean distance (the minimum length between the two ends of the segment) in the analyzed segments; logically, a higher ATI indicates a higher degree of AT [84].

It is therefore very clear that the aorta and large elastic arteries have a general inclination to become wider, stiffer, longer, and more tortuous with age, and the vascular kinking, in particular, is much more common in the aging population [82, 85]. The age-related burden on the ATI could be further corroborated by abdominal aortic segment mechanical tension rise, which in turn further supports vascular structural changes, as well as collagen-to-elastin ratio alteration [86]. Therefore, higher ATI in women has previously been justified by a reduction in the artery diameter and wall tension due to hormonal causes that may facilitate the progression of atherosclerosis in a gender-dependent manner, which is in line with a study published by Kamenskiy A. [85].

Of note, both AT and ATI as vascular parameters are still not in wide clinical use, since AT pathophysiology is not completely clear, as there persists a research gap regarding molecular pathways responsible for AT occurrence and its different phenotypes. Mainly, therefore, these vascular parameters remain today much more at the basic science stage.

It is also well documented that the most prevalent CV conditions are linked to tortuosity, including diabetes mellitus, aging, arterial hypertension, cigarette smoking, hyperlipidemia, and obesity/adiposity with increased body mass index [86, 87]. However, some controversies and debates surround this association. Some earlier studies reported that classical CV risk factors have a more direct impact on aortic geometry than on blood hemodynamics, as a consequence of calcification, stiffness, or the atherosclerotic process. The presence of atherosclerosis and calcification in the carotid and coronary arteries has been linked to the development of AT and also reported as its consequence, together with increased vascular stiffness, arterial hypertension, exacerbation of the atherosclerotic process, and hemodynamic disturbances of blood flow, as documented by Xie *et al*. in a 3D computational study [88, 89]. Thus, it is plausible that AT could precede coronary atherosclerosis or calcification, similar to what might occur in the carotid arteries.

The peripheral vascular tree is also severely affected by tortuosity changes, most commonly in the form of peripheral artery disease (PAD), whose primary feature is inadequate arterial perfusion of the limbs to meet physiological demands, largely due to atherosclerotic steno-occlusive disease and tortuosity changes [90]. This process is coupled with loss/degradation of elastic fibers and calcification and a subsequent increase in blood pressure in the elastic arteries during aging, which leads to altered blood hemodynamics, especially in the peripheral territories [91].

Finally, it is also very important to say that, in other, quite different vascular contexts, AT has been recognized and consolidated as a clinically relevant VA imaging marker. For example, in complex genetic arteriopathies syndromes (*i.e.*, Marfan, Loeys-Dietz, Ehlers-Danlos, *etc*.), elevated ATI can partially predict severe upcoming CV incidents and complications such as early/premature vascular surgery, arterial dissections, and CV mortality in general. The American Heart Association even recommends its assessment and radiological evaluation in pediatric and genetic arteriopathies to complement diameter-based risk stratification and restratification. Similarly, in cerebrovascular disease, carotid tortuosity degree correlates highly with the presence and quantity of small-vessel disease neuroimaging markers (*i.e.*, brain microbleeds/microhemorrhage, lacunar infarctions, microischemic vascular changes, diffuse white matter hyperintensities on T2w/FLAIR sequences—considered often as nonspecific vascular disease markers, *etc*.) and has been clearly linked to the occurrence of cervical artery dissections. These important relationships additionally highlight the prognostic and diagnostic value of AT in very specific vascular territories.

Left ventricular mass and function

Although LV mass is not, strictly speaking, an imaging vascular marker, it is strongly connected to the vascular system—ventricular remodeling correlates with vascular disease—so a brief account of these parameters is warranted in this article. LV hypertrophy is a primary pathological hallmark of adaptive LV remodeling, occurring as a natural, physiological response to increased pressure in the aorta. More importantly, it is closely associated with diverse major adverse outcomes and life-threatening complications (MI, stroke/TIA, ventricular arrhythmias, heart failure, coronary angioplasty/CABG, and sudden death) [92]. Regarding its connection with the VA process, LV

hypertrophy is, in most circumstances, a marker of late VA, since it usually occurs as a consequence of hemodynamic overload from preceding endothelial dysfunction and increased AS.

Cardiac magnetic resonance (CMR) is currently considered the most accurate and precise radiological method for LV mass (morphology) and hemodynamic (functional) evaluation—the so-called gold standard [93]. Despite that, transthoracic echocardiography is the most commonly used imaging option for rest evaluation thanks to its advantages (much more flexible and adjustable, less expensive, easier to repeat, and much more widely available).

In 2015, the ASE published reference values for LV mass and LV mass indexed to body surface area (LVMI) obtained by M-mode and two-dimensional (2D) echocardiography; these values were, however, significantly higher than the corresponding LVMI values obtained by steady-state free precession CMR in normal subjects [94-96]. This presumably reflects the reliance of these modalities on geometric assumptions, since the two imaging tools are not completely comparable. Similarly, Kusunose *et al*. reported the accuracy of transthoracic three-dimensional echocardiography (3DE) for LV mass measurement compared with CMR in 104 subjects (63 with ischemic and 41 with non-ischemic cardiomyopathy), noted some differences between the modalities, and concluded that 3DE is the most accurate and reliable echocardiographic method for measuring LV mass [97]. Nevertheless, this imaging technique still has not gained widespread clinical use in this context, due to the tedious manual tracing of both endo- and epicardial borders that is necessary for this examination. Thus, normal values for 3D LV mass are not provided in the ASE guidelines published in 2015, due to a lack of large sample investigations with normal LV mass values [94]. Nevertheless, the overall conclusion from this paragraph is that within the previous decades of research in LVH and LVMI has uncovered the prognostic importance of cardiac target organ damage, at least in part, and that it is of utmost importance that LV mass is accurately measured and calculated as this parameter has undeniably very important clinical and predictive implications [98, 99].

The EchoNoRMAL study was a large international multicentric cohort meta-analytic study (22,404 adult participants without previously documented clinical CV or renal disease, arterial hypertension, or diabetes mellitus, *etc*.), that performed detailed echocardiographic left heart measurements (including LA and LV size, LV mass, and systolic function, *etc*.) with the idea of developing ethnic-specific normative reference ranges and values. Importantly, sex- and/or ethnic-appropriate echocardiographic reference ranges and values are indicated for many measurements of LA and LV size, LV mass, and EF, and there were some clear differences between the reference values for LV volumes across the age range, sex, and ethnicity [100, 101].

Recently, clinical interest has grown in CMR "mapping" techniques, which provide direct and objective quantification of myocardial properties such as T1, T2, and T2* times, with potential for tissue characterization; these techniques facilitate the detection of diffuse myocardial abnormalities and subtle alterations practically undetect-

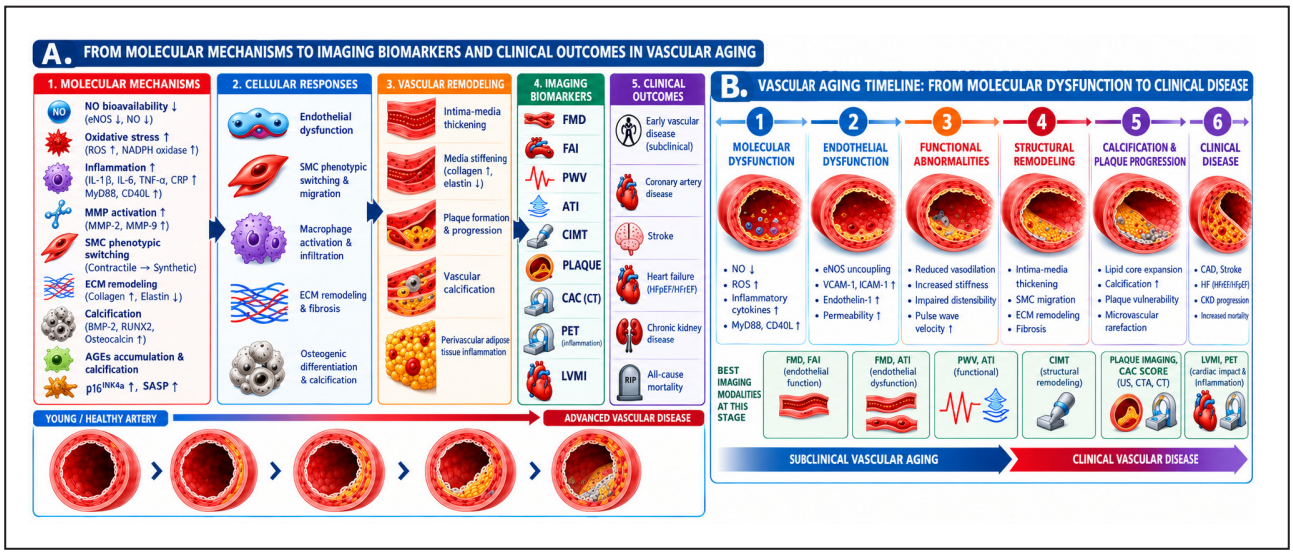


Figure 3. Overview of vascular aging, from molecular mechanisms to clinical outcomes. (A) The five-stage cascade, shown from left to right: molecular mechanisms (reduced NO bioavailability, oxidative stress, inflammation, MMP activation, smooth muscle cell phenotypic switching, ECM remodeling, calcification, advanced glycation end-product accumulation, and cellular senescence); cellular responses (endothelial dysfunction, smooth muscle cell phenotypic switching and migration, macrophage activation and infiltration, ECM remodeling and fibrosis, and osteogenic differentiation and calcification); vascular remodeling (intima-media thickening, media stiffening, plaque formation and progression, vascular calcification, and perivascular adipose tissue inflammation); imaging biomarkers (flow-mediated dilatation, fat attenuation index, pulse wave velocity, arterial tortuosity index, carotid intima-media thickness, carotid plaque, coronary artery calcium, PET-detected inflammation, and left ventricular mass index); and clinical outcomes (early vascular disease, coronary artery disease, stroke, heart failure, chronic kidney disease, and all-cause mortality). The bottom row depicts the progression from a young, healthy artery to advanced vascular disease. **(B)** The vascular aging timeline, from molecular dysfunction (stage 1) through endothelial dysfunction (stage 2), functional abnormalities (stage 3), structural remodeling (stage 4), and calcification and plaque progression (stage 5) to clinical disease (stage 6), with the most informative imaging modalities indicated for each stage; the lower bar indicates the transition from subclinical vascular aging to clinical vascular disease.

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able by visual assessment alone. Likewise, recent technical advances in 3D echocardiographic analysis allow semiautomatic determination of LVMI, which shows promise for easier implementation in routine clinical practice. Nevertheless, despite these studies and technical advances, one question remains open: how to define the optimal LVMI? Finally, Figure 3 is a pathology–assessment matrix linking initial molecular alterations and pathways to detectable pathological changes and their corresponding imaging tools (PWV, CIMT, FAI, LVMI, *etc*.), thereby addressing the question of what to look for and how to evaluate it.

Conclusions with future directions and potential course of action

Worldwide (particularly in the most developed countries), a global rapid general growth in the aged population is inevitably expected. This aging shift has very important clinical, pharmaceutical, and economic implications. The oldest subjects in our population (≥ 80 years old) are a rapidly increasing aging subgroup, and more than one-third of them experience important difficulties and limitations in everyday activities. The growing possibility of preventing or postponing systemic aging complications may be well understood by assessment of CV and stroke risks and prompt appropriate treatment of such risk markers.

The updated epidemiological studies and observations mentioned in this review, coupled with preclinical findings, have made it realistic to consider shifting the focus of prevention programs to more "upstream" targets—namely, shared molecular VA risk markers and the extrinsic (*i.e*., somatic and cellular mitochondrial alterations and mutations, oxidative stress with ROS formation, advanced glycation end-products, numerous active pro-inflammatory cytokines, *etc.*) and intrinsic (*i.e*., chromosomal telomere shortening, decrease in multiple growth factors, apoptosis, necrosis, *etc*.) mechanistic trajectories and pathways that may ultimately influence prevention outcomes. Additionally, it remains unclear how the upregulation or downregulation of many of the molecular pathways presented (*i.e*., NO signaling, CD40L, MyD88, and NETosis) specifically translates into measurable changes in VA imaging parameters (such as PWV, CIMT, or FAI). Many of these mechanisms therefore remain, at present, at the basic science stage. However, these molecular pathways should be regarded as targets for future investigations, and their elucidation could have very significant effects on the VA process, both physiological and particularly accelerated. Moreover, based on the evidence presented in this review, future clinical research should precisely define age-related normative curves for all the VA imaging parameters mentioned, which could together serve as a valid scale system for differentiating physiological from accelerated VA and make the decision on optimal therapy timing much easier.

More practically, future work should be transdisciplinary and translational: it should address the numerous vascular pathophysiological mechanisms involved in aging, identify new therapeutic targets for randomized clinical trials, explore the still poorly defined boundaries between CV age-related diseases, and develop broad strategies for systematic integration. With continued advances in CV basic science, physiology, pharmacology, epidemiology, and the relevant clinical specialties, researchers and clinicians will be better positioned to translate these findings into everyday practice. More and more attention worldwide is given to artificial intelligence (AI) development and its potential clinical applicability. Regarding this topic of VA, Shin H. has published an article regarding the potential of the so-called XGBoost system as a useful VA assessment model (using XGBoost regression model) based primarily on photoplethysmogram features in 752 volunteers, and further exploring its key features through an explainable AI method [102]. This exemplary innovative approach has potential for further development.

We live at a time when scientific discoveries are providing valuable insights into human biology at an unprecedented rate. Vascular biology was recognized as a frontier long ago but has come into real prominence over the last 20–30 years, as the crucial molecules that mediate the essential functions of blood vessels have been identified and more precisely defined. Besides, since aging is an endothelium-based disease, the 1998 Nobel Prize in Medicine award to Dr. Robert Furchgott, Dr. Louis Ignarro, and Dr. Ferid Murad for their pioneering work in the discovery of NO as a novel important mediator of many biological functions reflects a well-deserved appreciation of the entire field, and gave a new impetus to the search for compounds that either imitate its action or boost its production in the CV system. Research on the role of NO has continued in the last 20 years, and is still ongoing, and it is now clear that, in addition to the CV system, NO is implicated in the function and disease of several other organs and systems as well. From a more practical point of view, several basic research observations are now yielding novel therapeutic principles, which are being pursued in randomized clinical trials.

Therefore, future translational vascular investigations and research (particularly VA and AS investigations) should optimally: 1. enhance VA clinical assessment methodology; 2. promptly recognize and identify specific VA and AS phenotypes and endotypes (new ones); 3. decipher in detail the possible subtle molecular mechanisms of how state-of-the-art technologies work and recently recognized hazard factors (*e.g.*, sedentary life, chronic psychosocial stress, constant surrounding high-level noise at living place, air pollution, *etc*.); 4. develop tailored well-organized prevention and therapeutic approaches. In line with this latter context, there is a global call for an interdisciplinary and translational scientific framework broadening for further long-lasting, intensive investigation activity into the field of VA and AS, and a subsequent breakthrough in this field.

Declarations

Author contributions: The author contributed solely to the article.

Availability of data and materials: All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Ethical approval and informed consent: Not applicable.

Conflicts of interest: Not applicable.

Financial support and sponsorship: None.

AI and AI-assisted tools statement: I acknowledge the use and help of ChatGPT for making Figures 1-3. I have verified and edited the final content. The AI and AI assisted tools were not used for writing this article.

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Cite this article as: Petrović DJ. Pathogenesis and pathobiology of imaging vascular biomarkers during the aging process: a narrative review. *Aging Pathobiol Ther*, 2026, 8(3): 293-308. doi: 10.31491/APT.2026.09.234