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Noninvasive Techniques for Tracking Biological Aging of the Cardiovascular System

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ABSTRACT

Population aging is one of the most important demographic transformations of our time. Increasing the "health span"—the proportion of life spent in good health—is a global priority. Biological aging comprises molecular and cellular modifications over many years, which culminate in gradual physiological decline across multiple organ systems and predispose to age-related illnesses. Cardiovascular disease is a major cause of ill health and premature death in older people. The rate at which biological aging occurs varies across individuals of the same age and is influenced by a wide range of genetic and environmental exposures. The authors review the hallmarks of biological cardiovascular aging and their capture using imaging and other noninvasive techniques and examine how this information may be used to understand aging trajectories, with the aim of guiding individual- and population-level interventions to promote healthy aging.

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ABBREVIATIONS AND ACRONYMS

AI = artificial intelligence

CCT = cardiac computed tomography

CHIP = clonal hematopoiesis of indeterminate potential

CMR = cardiac magnetic resonance

CVD = cardiovascular disease

ECG = electrocardiographic

LV = left ventricle/ventricular

LTL = leukocyte telomere length

LVEF = left ventricular ejection fraction

RA = right atrial/atria/atrium

People across the world are living to older ages. Globally, the population >65 years is growing faster than any other age group.[1] In 2020, the number of people >60 years outnumbered children <5 years.[1] Between 2019 and 2050, the population >80 years is expected to almost triple, from 143 million to 426 million.[1]

Population aging is one of the most important demographic shifts of our time, with implications across all societal structures. A longer life brings many opportunities. However, the degree of benefit is dependent on the maintenance of health. There is increasing focus among public health experts on strategies to increase the "health span": the proportion of time spent in good health.

At a biological level, aging is a gradual process of molecular and cellular damage accrued over many years, leading to declines in physical and mental capacity, age-related illnesses, and death. The trajectory of biological aging is complex and nonlinear and has a variable relationship to chronological age.[2] Indeed, people of the same chronological age may have very different biological ages, determined by genetic and environmental exposures occurring throughout the life course.

The global burden of age-related illnesses is increasing in parallel to aging populations.[3] Among these, cardiovascular diseases (CVDs) are a major source of ill health and early death in older people. Biological aging has distinct manifestations across all components of the cardiovascular system (**Central Illustration**). Noninvasive imaging and molecular techniques can provide a window into the form and function of the aging heart and allow tracking of biological cardiovascular aging. This information can be used to evaluate healthy aging patterns, determinants of aging trajectories, and potential strategies to promote healthy cardiovascular aging.

In this review, we provide a state-of-the-art perspective on the concept of biological aging and its determinants, age-related alterations of the cardiovascular system, imaging and other noninvasive techniques to capture and track the aging heart, the role of big data and molecular markers in understanding biological cardiovascular aging, and a discussion of emerging technologies and future directions.

THE CONCEPT OF BIOLOGICAL AND HEALTHY AGING

IS AGING PHYSIOLOGICAL AND INEVITABLE?

The question of whether aging is purely a physiological process and inherently inevitable has been a subject of extensive debate. Recent research is reshaping our understanding through identification of various factors which appear to alter the aging trajectory (**Figure 1**).

Growing evidence highlights that cellular senescence, a key aspect of aging, is not solely tied to time but responds to various stressors.[4] The role of mitochondrial dysfunction in biological aging similarly blurs the line between natural degeneration and modifiable processes.[5]

Genetic and epigenetic investigations reveal intricate mechanisms influencing aging rates. Centenarian studies emphasize the impact of genetics on aging, especially in old age.[6] Epigenetic changes, shaped by the environment, emphasize that aging is not solely tied to time.[7]

Some researchers have proposed that it may be possible to eliminate or reverse harmful cell modifications, even chemically, effectively resetting a cell's biological age to "ground zero,"[8,9]—a groundbreaking concept. Emerging works suggests that lifestyle interventions such as caloric restriction and exercise may slow aging process.[10,11]

Thus, recent discoveries reveal the complex interplay between biology and time in aging.[12] These findings open doors to interventions that could extend the health span and reshape the aging trajectory.

WHEN DOES AGING BECOME PATHOLOGIC?

The distinction between "normal" and pathologic aging is not always clear cut. Although physiological declines in organ function are expected with increasing age, a sudden or rapid deterioration warrants further investigation to exclude underlying disease processes.

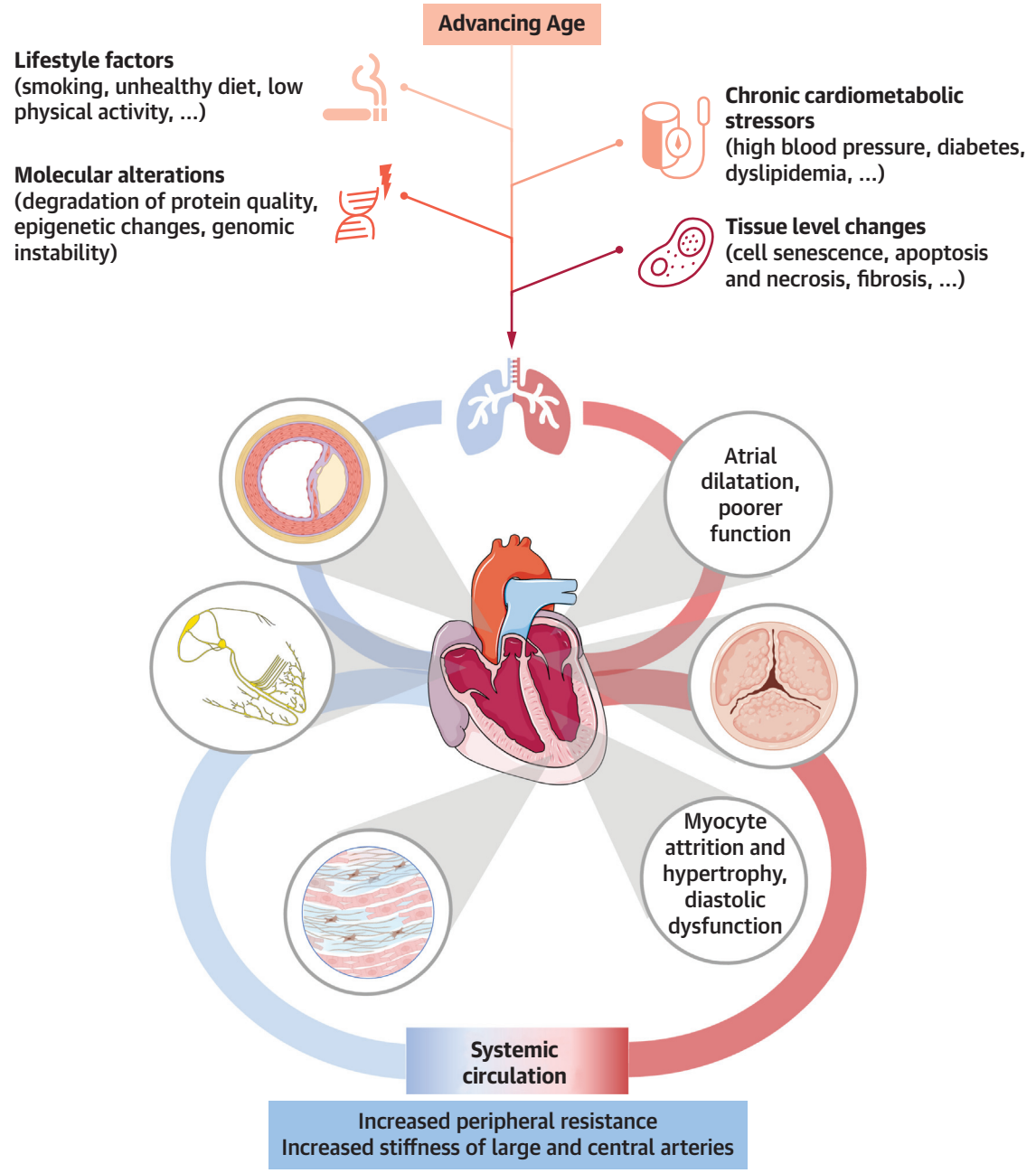
Thus, it is the rate at which aging occurs that is of most interest and can be used to measure healthy aging, identify individuals on an adverse aging trajectory, and detect abrupt deviations in aging trends that may indicate disease occurrence.

Understanding the determinants of biological aging and the factors that may modify these trends is important in defining public health and therapeutic strategies to promote healthy aging and the period of life spent in good health.

MODIFICATION OF AGING TRENDS WITH DISEASE.

Increasing age is a risk factor for chronic diseases and disability. A recent study among 2 large population cohorts demonstrated that greater biological aging (estimated using a circulating biomarker-based model) mediated the associations of unhealthy lifestyles with adverse health outcomes, including CVDs, cancers, and death.[13]

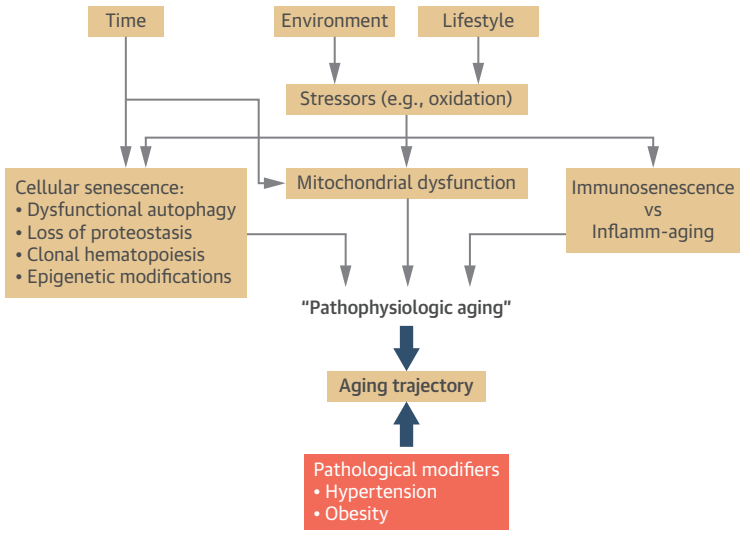
CENTRAL ILLUSTRATION **Overview of Age-Related Changes Across the Cardiovascular System**



Raisi-Estabragh Z, et al. J Am Coll Cardiol Img. 2024;17(5):533–551.

One explanation for the role of greater biological aging in mediating adverse health outcomes relates to chronic inflammation state ("inflammaging") and immune dysfunction (immunosenescence). Once thought to be solely detrimental, an emerging paradigm is that the dynamic interaction between inflammaging and immunosenescence could be adaptive.[14] According to this hypothesis, a chronic proinflammatory state could be viewed as a defense mechanism if it is well regulated. If an individual succeeds in adapting (or demonstrates resilience from a health challenge), the trajectory to age-related pathologies can be delayed. On the contrary, perturbation of this equilibrium may accelerate aging to earlier onset of chronic diseases.[15]

FIGURE 1 Schematic of Factors That Influence the Aging Trajectory



Biological aging and acceleration of its processes can predispose to a multitude of age-related illnesses through different postulated mechanistic pathways. In a cyclic fashion, the occurrence of disease in turn adversely alters the aging trajectory, accelerating biological aging and predisposing to further disease accumulation. Indeed, multimorbidity has been highlighted as a major emerging public health challenge closely linked to aging.[16]

EXPECTED AGE-RELATED CHANGES IN THE CARDIOVASCULAR SYSTEM

MOLECULAR AND CELLULAR HALLMARKS OF CARDIOVASCULAR AGING. At a molecular level, the aging-related deterioration of the cardiovascular system can be grouped into a series of fundamental processes that either directly drive cardiovascular aging ("primary" hallmarks) or reflect adaptations to

FIGURE 2 Age-Related Changes of Myocardial Tissue

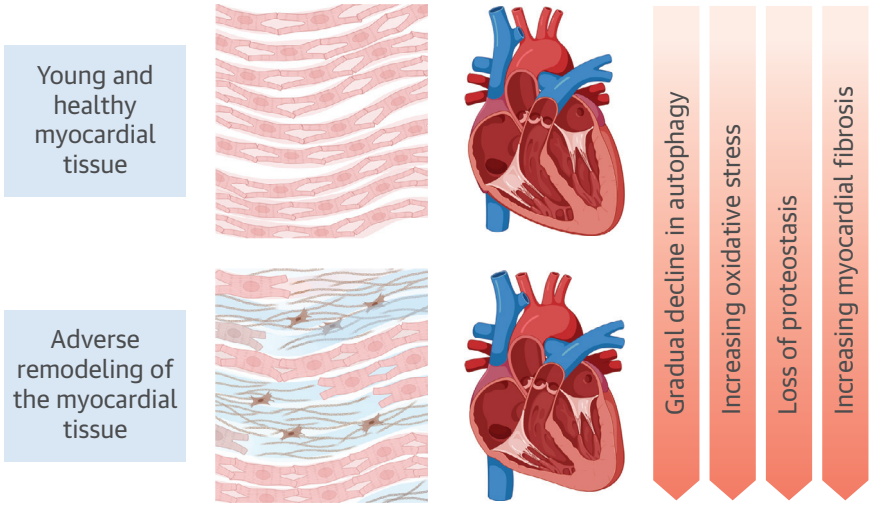
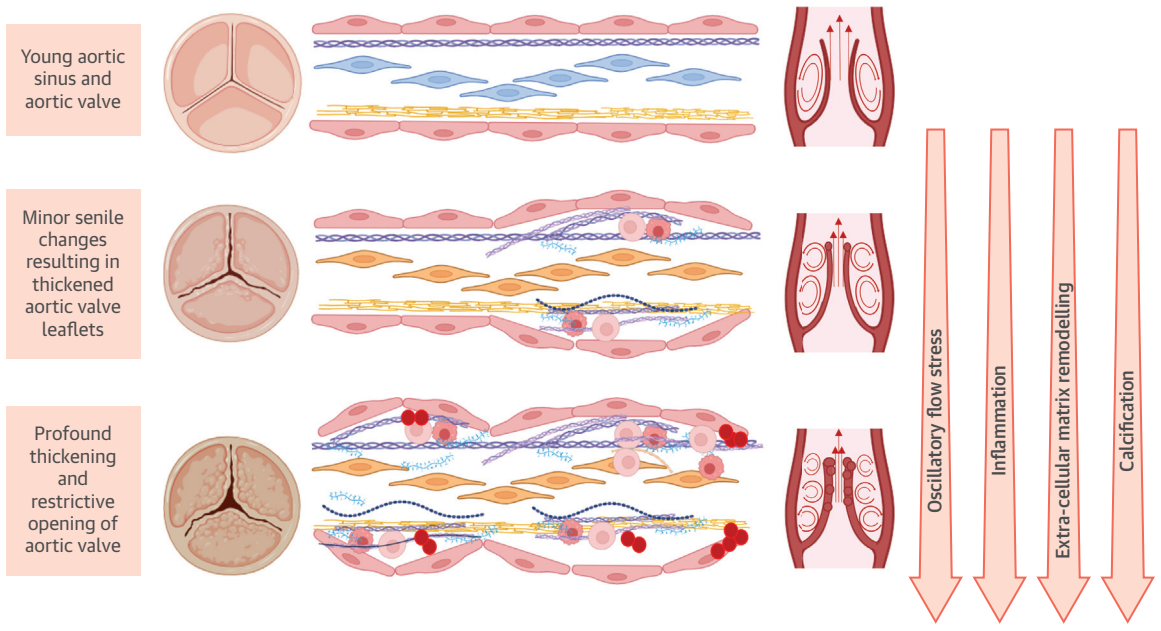


FIGURE 3 Aging-Related Pathophysiological Characteristics of Valvular Heart Disease



Key contributory factors to valvular aging include abnormal flow-associated valve stresses and inflammation. These lead to loss of elasticity, thickening, increased fragility, calcification, and extracellular matrix remodeling.

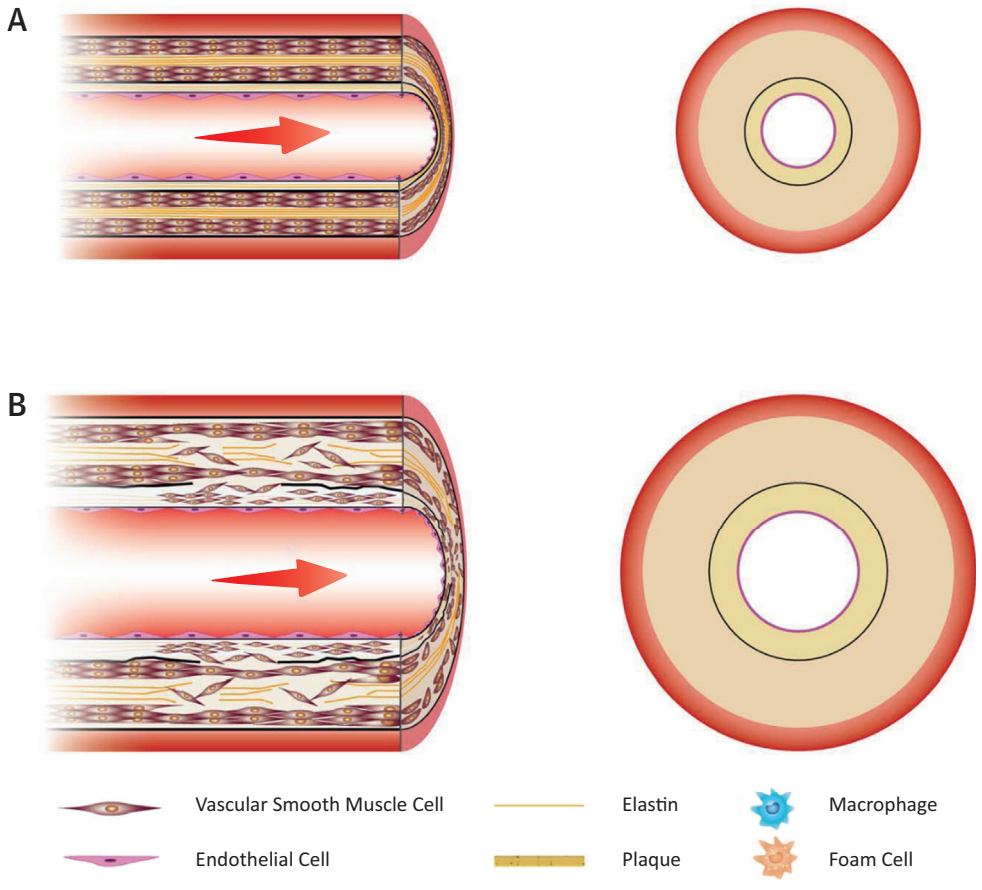
these primary processes ("antagonistic" hallmarks).[17] The primary hallmarks include dysfunctional autophagy, loss of proteostasis, genomic instability (eg, clonal hematopoiesis), and epigenetic modifications. Antagonistic hallmarks include mitochondrial dysfunction, neurohormonal dysregulation, and cell senescence (eg, through telomere attrition).[17] The accumulation of these processes can precipitate the onset of organ dysfunction.

AGE-RELATED REMODELING MANIFESTATIONS ACROSS CARDIOVASCULAR STRUCTURES. **Myocardium.** Aging affects individual myocardial tissue components (eg, cardiomyocytes, cardiac fibroblasts, vascular smooth muscle cell, endothelial cells, cardiac stem cells) and the overall myocardial tissue composition (**Figure 2**). Animal studies demonstrate myocyte attrition and cellular hypertrophy with increasing age, thereby illustrating that the aging myocardium is composed of a smaller number of hypertrophied cells.[18] This is accompanied by adverse extracellular matrix remodeling and increased fibroblast activity, resulting in structural alterations and myocardial fibrosis.[19] Senescent cardiomyocytes may induce cell-cycle arrest in neighboring healthy cells via paracrine signaling, thereby promoting inflammation and dysfunction.[20]

Molecular mechanisms, including dysfunctional autophagy and production of reactive oxygen species, play substantial roles in fostering cardiac senescence. Autophagy is a vital element to maintain cell homeostasis, whereby cells clean out damaged components and recycle them.[21,22] The aging-associated decline of autophagy is associated with cardiomyocyte dysfunction and death, which in turn cause age-related myocardial diseases manifesting as heart failure.[21,23] An excess of reactive oxygen species can damage macromolecules, leading to cellular and organ dysfunction. Although reactive oxygen species have been implicated in CVDs, evidence on the use of antioxidants to halt aging is inconclusive.[19] The role of other molecular pathways such as telomere attrition and altered insulin-like growth factor 1 signaling have also been implicated in cardiac aging-related structural changes and dysfunction.[24-26]

The intrinsic aging-related deterioration of myocardial function is aggravated by gradual and chronic increases in afterload (eg, due to aging-associated vascular and valvular stiffening). The age-related histologic and structural changes steer the myocardium toward functional decrements and increased vulnerability to disease with increasing age.

FIGURE 4 Cellular Changes of Vascular Aging



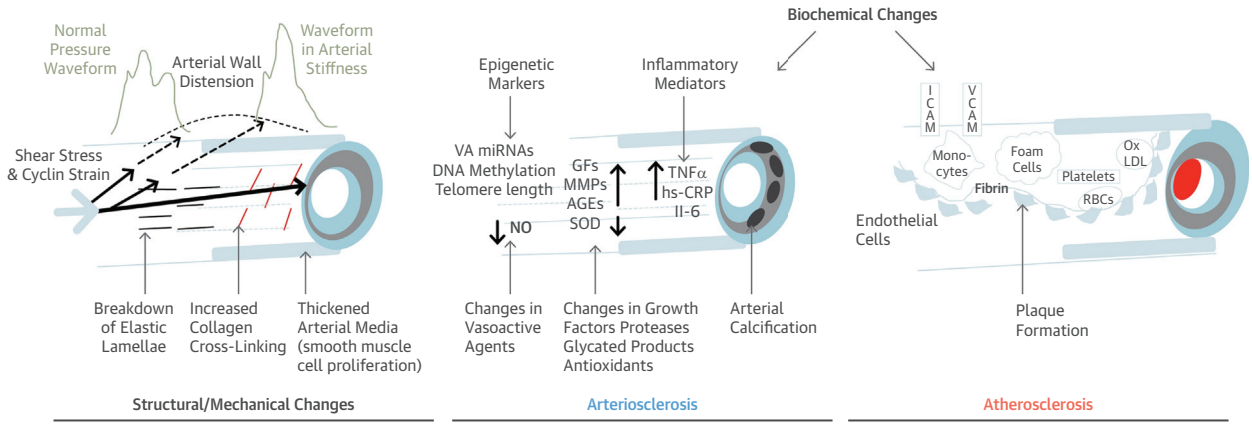
(A) Normal artery. (B) Aged artery. This process is characterized by thickening of the vessel wall (especially the subendothelial layer), vascular smooth muscle cell migration and invasion, extracellular matrix deposition and fragmentation of elastin. Modified with permission from Xu et al,[41] licensed under CC BY 4.0.

Valves. Aging has a significant impact on crucial heart valve components, including valve endothelial and interstitial cells (**Figure 3**). Valvular endothelial cells constitute a surface monolayer critical for valve function, while the interstitial cells uphold the extracellular matrix. Aging valvular endothelial cells have lower proliferation rates, reduced nitric oxide production, increased reactive oxygen species release, and reduced cell membrane self-repair in response to stretch-induced injury.[27] Additionally, aging is accompanied by reduced density of endothelial cells, leading to decreased cell-cell interactions and increased permeability. Disrupted valvular endothelial-interstitial cell communication results in increased cellular migration, proliferation, and extracellular remodeling.[28] This results in a gradual increase in elastic and collagen fibers across valve types with aging. Dysfunctional valvular endothelial cells can further lead to the differentiation of valvular interstitial cells into pro-calcific cells, precipitating the onset of valve calcification.[29]

Thus, increasing age is associated with greater thickening, stiffening, degeneration, calcification, and impaired repair mechanisms of cardiac valves. These alterations drive increased burden of valvular heart disease in elderly patients. The most common aging-associated valvular heart diseases are aortic stenosis, mitral regurgitation, and aortic regurgitation.[30]

Conduction system. In the sinoatrial node, aging results in increased fibrosis,[31] reduced expression of gap junctional protein Cx43,[32] and altered ionic currents, including reduced L- and T-type Ca^{2+} and I_f currents.[33,34] These changes are associated with

FIGURE 5 Mechanisms of VA and Their Distinction (and Eventual Evolution) to Arteriosclerotic and Atherosclerotic Processes



AGE = advanced glycation end product; GF = growth factor; hs-CRP = high-sensitivity C-reactive protein; ICAM = intercellular adhesion molecule; Il = interleukin; miRNA = micro-RNA; MMP = matrix metalloproteinase; NO = nitric oxide; Ox LDL = oxidized low-density lipoprotein; RBC = red blood cell; SOD = superoxide dismutase; TNF = tumor necrosis factor; VA = vascular aging; VCAM = vascular cellular adhesion molecule. Reproduced with permission from Climie RE, Alastruey J, Mayer CC, et al. Vascular ageing: moving from bench towards bedside. *Eur J Prev Cardiol.* 2023;30(11):1101-1117. doi:10.1093/eurjpc/zwad028, licensed under CC BY 4.0.

slowing of both early diastolic depolarization[31,33] and action potential propagation across the sinoatrial node,[32] leading to well-described age-related decreases in intrinsic and maximum heart rates.[32,33] There is a resultant increase in incidence of sick sinus syndrome with age.[35] In the atrioventricular node, age-related changes include prolongation of atrioventricular nodal effective refractory periods.[36,37] Replacement fibrosis has been reported in the His bundle and left bundle branch,[38] while alterations in repolarization currents occur in Purkinje fibers.[39] These changes combine to lead to significantly increased rates of pacemaker implantation in elderly individuals.[40]

Vasculature. The age-related deterioration of vascular structure and function predominantly involves the arteries (**Figure 4**). Mechanisms of vascular aging have commonalities with arteriosclerosis and atherosclerosis (**Figure 5**), with some differences across the vascular tree. In the aorta, vascular aging involves the intima and is characterized by reductions in elasticity and diameter,[41] which contribute to increased systolic and pulse pressures and reduction in compliance. Muscular arteries, including the carotid and femoral, undergo dilatation, with medial thickening being the preponderant cause of increased intima-media thickness.[41]

Two major age-related changes affect vascular function: arterial stiffening (reflecting increased fibrous tissue with elastin fragmentation) and endothelial dysfunction. Arterial stiffening predominantly affects the central rather than peripheral arteries,[42] leading to increased pulse-wave velocity[43] and ankle-brachial index as well as elevated systolic and pulse pressures. Increased wave velocity in proximal vessels leads to earlier reflected pressure waves, causing augmentation of central pressure and increased afterload.[44] The lower peripheral/central pulse pressure ratio reduces pressure amplification, with consequences for peripheral perfusion and potentially causing microcirculatory damage.[45] Similar to arterial stiffening, endothelial dysfunction is linked to risk factors but may occur with increasing age even in their absence.[46] Although this pathology is recognized as an atherogenic initiator, other consequences of endothelial dysfunction include disturbances of vasodilation and constriction, vascular growth, thrombosis, and inflammation.[47]

SEX DIFFERENCES IN AGE-RELATED CARDIOVASCULAR REMODELING. **Table 1** delineates the sex-specific differences in cardiac structure and remodeling. These differences likely reflect variations in exposure to cardiovascular risk factors and hormonal changes pre- and postmenopause. Men are more prone to left ventricular (LV) hypertrophy and fibrosis, often culminating in eccentric myocardial remodeling.[18-50] Women tend to develop concentric patterns of LV hypertrophy and present more often with diastolic dysfunction.[51-53] Contemporary research underscores the variances in vascular and valvular characteristics

TABLE 1 Sex-Specific Differences in Cardiovascular Aging

Age-Related Alteration Across Cardiac Structures	Male Characteristics	Female Characteristics	Notes
Myocardium			
LV hypertrophy, wall thickening	More common	Less common, accelerated wall thickening to exposure	LVH is often a response to hypertension, which is more prevalent in aging men. In contrast, the relative LVH in response to risk factor exposure is greater among women.
LV fibrosis	Diffuse subclinical interstitial fibrosis	Less common	Subclinical interstitial myocardial fibrosis is driven by declining sex hormone levels in men.
LV morphology	Eccentric remodeling	Concentric remodeling	Women have smaller LV dimensions even after accounting for body size, and they present with greater relative wall thickening.
Diastolic dysfunction	Less prevalent	More prevalent	Women are more likely to develop diastolic dysfunction because of smaller ventricular size and altered relaxation properties.
Systolic function	Generally preserved, earlier onset decline HFrEF phenotype	Later onset of impaired systolic pump function HFpEF phenotype	Women may maintain systolic function longer than men as a consequence of LV structural remodeling.
Valves			
Aortic stenosis	More common	Less common	Men are at a higher risk for calcific aortic valve diseases.
Mitral valve leaflet thickening, prolapse, calcification risk	Less common	More common	Prevalence is higher in women, possibly related to connective tissue differences.
Vasculature			
Arterial stiffness	Stable, progressive increases with aging	Accelerated increase postmenopause	Estrogen loss in women may contribute to a more significant increase in arterial stiffness.
Coronary artery disease	Earlier onset, heightened risk for morbidity and mortality because of long-term exposure to risk factors and chronic lipid accumulation	Later onset but faster progression postmenopause	Men are more likely to develop CAD at a younger age, but women can present with accelerated plaque formation postmenopause.

CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVH = left ventricular hypertrophy.

between the sexes, illustrating that men face a progressively worsening risk of calcific aortic valve diseases and arterial stiffness throughout the life course,[54] whereas women are more susceptible to mitral valve alterations and exhibit an accelerated increase in arterial stiffness postmenopause.[52]

NONINVASIVE MARKERS FOR TRACKING PHYSIOLOGICAL AGING

Cardiovascular aging leads to distinct remodeling patterns and progressive decline in structure and function, which may be captured using cardiovascular imaging techniques, as summarized in Table 2.

MYOCARDIUM. Hypertrophy. LV wall thickness and overall myocardial mass can be quantified using echocardiography or cardiac magnetic resonance (CMR). Although LV hypertrophy was traditionally considered an attribute of aging, longitudinal studies now demonstrate that a large proportion of age-associated hypertrophy relates to a higher burden of vascular risk factors in elderly individuals.[55] This perspective is supported by studies in healthy populations, which show that healthy individuals maintain relatively stable myocardial mass between the ages of 20 and 70 years.[56-60] These observations are in keeping with our understanding of myocardial aging at a cellular level with attrition of cardiomyocytes and cellular hypertrophy resulting in either no net change or reduction of measured myocardial mass. Healthy myocardial aging trends may be similarly disrupted by transthyretin amyloidosis, most common in older individuals, which characteristically results in increased LV wall thickness and expansion of the extracellular matrix, captured by CMR or through amyloid tracers.[61]

Fibrosis. Cardiomyocyte loss with aging is accompanied by an expansion of the extracellular matrix and increased fibrosis,[19] leading to stiffness and impaired function.[62] CMR uniquely allows the noninvasive assessment of myocardial tissue characteristics using mapping and contrast enhancement techniques. Aging is associated with diffuse myocardial fibrosis, which may be captured by increases in myocardial native T1 mapping or extracellular volume quantification.[63] Population-based studies demonstrate the prognostic value of elevated myocardial T1, even in individuals without baseline CVD.[64] Age-related fibrosis of the left atrium is also described, although its quantification is not well established,

TABLE 2 Key Imaging Markers and Examples for Assessing Cardiac Aging Trajectories

Imaging Marker	Description	Imaging Modalities	Imaging Parameters	Example Range From the Published Reports[a]
Myocardial mass	Myocardial mass decreases in aging population with low risk factor burden Mass may increase or stagnate in aging population with high risk factor burden Increased (relative) LV wall thickness	Echocardiography, CMR	LV mass LV wall thickness LV mass/volume ratio	LVMi using CMR in population with low risk factor burden[153] 50-60 y: 70-72 g/m^2 60-70 y: 67-70 g/m^2 >70 y: <67 g/m^2
Myocardial tissue composition	Slight increase of ECV with advancing age Relative increase fibrosis partially due to loss of cellular components	CMR	Native T1 mapping	Native T1 mapping at 1.5 T (shMOLLI) in healthy population[64] 55-64 y: 917 ± 31 ms 65-74 y: 921 ± 33 ms 75-84 y: 926 ± 32 ms
			ECV	ECV at 1.5 T (MOLLI) in healthy population[154] 54-63 y: 25% ± 3% 64-73 y: 25.5% ± 3% 74-83 y: 26.5% ± 3% >84 y: 28% ± 4%
Ventricular volumes	Gradual decline in ventricular volumes	Echocardiography, CMR	LV end-diastolic volume LV end-systolic volume LV stroke volume	LVEDVi using CMR in healthy population[60] 20-40 y: 78-83 mL/m^2 40-65 y: 65-77 mL/m^2 >65 y: 58-72 mL/m^2
Systolic function	Resting LV systolic function remains maintained for a longer time	Echocardiography, CMR	LVEF LV global function index	LVEF using CMR in healthy population[60] 20-40 y: 58%-67.5% 40-65 y: 59%-66.5% >65 y: 59%-70%
LV strain	Gradual decline of GLS	Echocardiography, CMR	GLS (GCS and GRS have larger heterogeneity)	LV GLS using speckle-tracking echocardiography in healthy population[155] 31-40 y: −16.1% ± 2.1% 41-50 y: −15.7% ± 2.8% 51-60 y: −15.6% ± 2.2% 61-82 y: −15.3% ± 2.5%
Diastolic function	Impaired myocardial relaxation and increased stiffness	Echocardiography	E/A ratio, e′, E/e′ ratio	E/e′ ratio using tissue Doppler imaging Echocardiography in healthy population[156] 20-29 y: 6 ± 2 cm/s 30-39 y: 6.5 ± 2 cm/s 40-49 y: 7 ± 2.2 cm/s 50-59 y: 8.2 ± 2.5 cm/s 60-69 y: 9 ± 2.7 cm/s 70 79 y: 9.2 ± 3 cm/s
LA volumes and function	Increase in volumetric dimensions and slight functional deterioration of the LA	Echocardiography, CMR	LA diameter, LAV, LAEF	3D maximum LAVi in healthy population[157] 18-40 y: 16-41 mL/m^2 40-65 y: 16-46 mL/m^2 >65 y: 18-48 mL/m^2

Key imaging markers used to assess the trajectories of cardiac aging are presented, including myocardial mass, tissue composition, cardiac chamber volumes, and function, with example references to specific age-related changes reproduced from related publications. [a]Examples are from White male samples.

CMR = cardiac magnetic resonance; ECV = extracellular volume; GCS = global circumferential strain; GLS = global longitudinal strain; LA = left atrial/atrium; LAEF = left atrial ejection fraction; LAV = left atrial volume; LAVi = left atrial volume index; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVMi = left ventricular mass index; other abbreviations as in Table 1.

and it may be better captured through surrogate markers.

Decrease of ventricular volumes. Ventricular volumes gradually decrease with aging.[60] The first-line modality for volumetric quantification is echocardiography, but CMR offers superior endocardial border definition and whole-heart coverage. This gradual decrease of LV volumes alongside relative stability of LV myocardial mass translates to a tendency toward a concentric LV remodeling pattern with increasing age,[58] particularly among women.[52]

Systolic and diastolic function. The architecture of the LV myocardium comprises layered spiral clockwise and anticlockwise arrangement of myofibers.[65] Together, these result in a contractile action that produces simultaneous narrowing, shortening, and twisting of the LV in systole and widening, lengthening, and untwisting in diastole.[65] Interruption of myofiber interactions results in compromise of diastolic and systolic function. Capture and quantification of cardiac function and all its intricacies is challenging, and interpretation of observed trends

requires deep understanding of the LV form and cardiac mechanics.

As individuals age, there is a noted decline in ventricular diastolic function due to impaired myocardial relaxation and increased stiffness. The role of several pathways is implied in this process, including reduced troponin phosphorylation, altered Ca^{2+} handling, ventricular stiffening of senescent myocardium, and increasing fibrosis, contributing to diastolic dysfunction.[19] This aging-related reduction of diastolic function is best captured on echocardiography, using a combination of surrogate markers to detect elevated LV filling pressures and their hemodynamic consequences.[66]

Interpreting trends in systolic function is more challenging, as failure of one muscle fiber layer may be compensated by another, giving the impression of maintained or even supranormal global systolic function. Left ventricular ejection fraction (LVEF) is the most widely used metric to quantify cardiac function. Although useful for detection and prognostication in the setting of heart failure, LVEF does not capture the early granular myofiber alterations related to aging.[67] Compensatory adaptations of the radial myofiber layer, a tendency toward concentric remodeling, and the geometric assumptions in the calculation of LVEF mean that it paradoxically overestimates cardiac function in the aging heart.[68] Indeed, growing evidence from population cohorts demonstrates an association of supranormal LVEF with higher risk for adverse outcomes.[69] Studies of healthy populations report either little change in LVEF with increasing age or a slight increasing trend.[60] LV global function index—the ratio (×100) of LV stroke volume to LV global volume, with the latter defined as the sum of mean LV volume and myocardial volume—has been proposed as an alternative measure of LV function. This includes a correction for LV structure, thereby removing some of the limitations of LVEF and appears to show a linear association with health. The utility of global function index has been demonstrated in large population samples.[70,71]

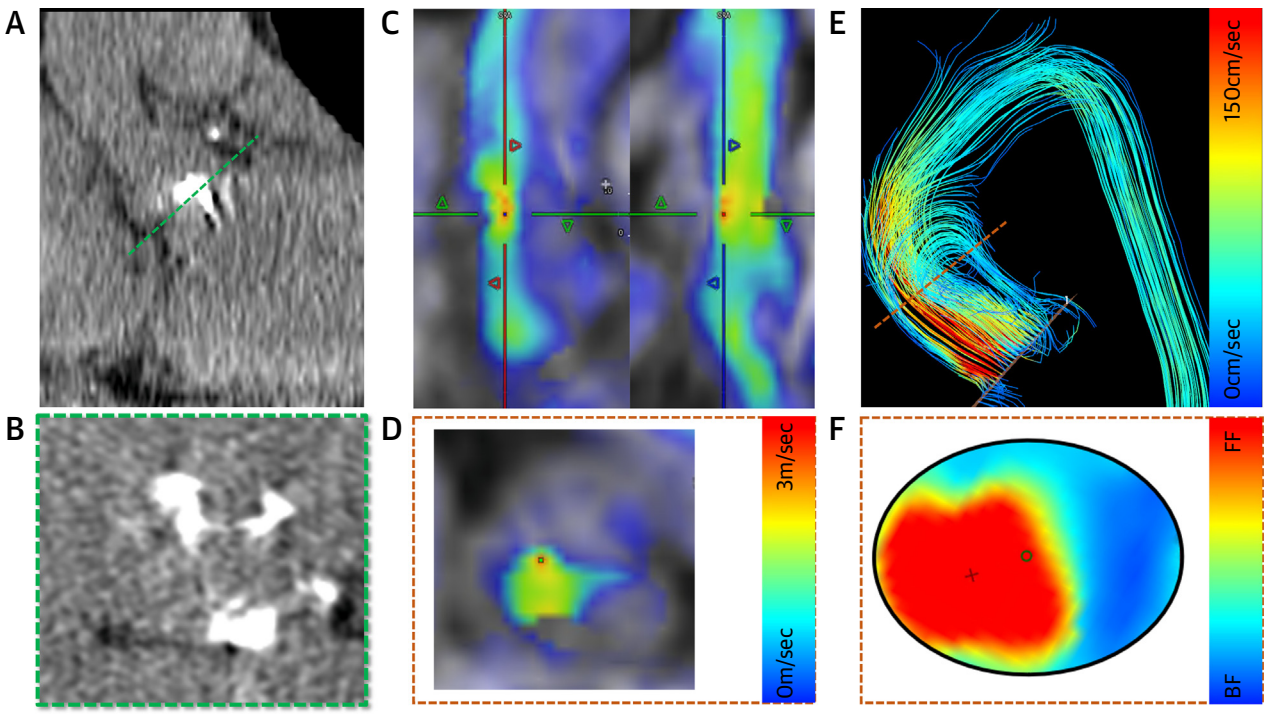
Measures of deformation (or strain) aim to quantify myocardial shortening and have been proposed as more sensitive and accurate measures of contractile function. It is proposed that these measures may provide information about fiber level function, allowing the detection of subtle changes and tracking of trends in contractile function. Strain can be measured at a global or local level, with different measures obtained for longitudinal, radial, and circumferential strain, representing the function of different myofiber layers. This is informative, as biological studies have suggested a sequential pattern of myofiber failure, which may be captured using strain imaging.[72] Longitudinal strain is arguably the most sensitive for the detection of early disease, independent of LV hypertrophy, and varies within levels of ejection fraction in a way that circumferential strain does not.[73] The longitudinal myofiber layer has been highlighted as the first layer to experience impairment; this is typically accompanied by compensatory increase in radial fiber layer contractility, which over time also becomes impaired. Deformation may be assessed using speckle-tracking echocardiography[72] or dedicated CMR techniques, including myocardial tagging, strain-encoded imaging, or feature tracking.[74] There are major variations in strain measurements across methods, vendors, and even software packages provided by the same vendor.[75] Considering these issues, the echocardiography community has established common standards for 2-dimensional speckle-tracking echocardiography.[76] The standardization of CMR-derived strain requires development to allow universal comparability of the technique.

Myocardial torsion can be measured using similar techniques to strain using echocardiography and CMR and aims to capture the twisting and untwisting motion of the heart with contraction.[77] Although torsion has been presented as a potential early indicator of cardiac function, descriptions of its relationship to health and disease are limited.[77] Greater study of this metric is required to determine its usefulness for tracking cardiovascular aging.

Left atrial volumes and function. Echocardiography and CMR stand as the main instruments for overseeing atrial diameter alterations in aging. Increases in volumetric dimensions and functional deterioration of the left atria have been observed with increasing age.[78] The reservoir and conduit functions are particularly affected.[79] Using atrial strain could potentially offer a more nuanced approach in detecting age-associated functional declines in the atria as well as diastolic LV function.[80]

Right atrial structure and function. Age-related changes in right atrial (RA) morphology and inflow pattern have been observed in a few studies. With aging, there is a shift in the axis of the caval veins, with the outlets of the superior and inferior caval veins facing each other in younger subjects, and lateralization occurring in older subjects.[81] This shift in the caval vein axis can affect the blood flow pattern in the RA. In younger subjects, the blood flow of the RA typically shows a clockwise rotating helix without signs of turbulence. However, in older subjects, this rotation may be absent, and turbulence is significantly more

FIGURE 6 **Multimodality Imaging in Aortic Stenosis: An Age-Related Disease**



(A,B) Noncontrast computed tomography in a 75-year-old man shows significant calcium burden on the aortic valve, consistent with at least moderate aortic stenosis. (C,D) Four-dimensional flow maximum transvalvular velocity on magnetic resonance imaging was 2.7 m/s, consistent with moderate aortic stenosis. (E,F) Four-dimensional flow aortic streamlines at peak systole demonstrating vortex formation near the inner curvature of the aortic root and resulting in a loss in aortic conduit function due to retrograde flow (F).

frequent.[81] Additionally, mean and peak systolic blood flow in the caval veins decrease with age.[81] Furthermore, progressive RA dilation and an increase in sphericity have been observed from healthy volunteers to patients with paroxysmal and persistent atrial fibrillation.[82]

VALVE STRUCTURE AND FUNCTION. When it comes to valvular aging, several key imaging biomarkers are commonly assessed using noninvasive imaging modalities, such as echocardiography,[83] CMR, and cardiac computed tomography (CCT). Five key imaging biomarkers of valvular aging are described in the following discussion.

Valvular thickening. Echocardiography,[84] CMR,[85] and CCT[86] can all detect and quantify the thickening of valve leaflets. The loss of elasticity renders the valves incompetent to cope with increased hemodynamic stresses, and this eventually leads to valvular incompetence and/or stenosis (Figure 6).

Calcification. Calcification is a hallmark of valvular aging and can be visualized using echocardiography and CCT. Calcium deposits accumulate on the valve leaflets, causing them to become rigid. The degree of calcification, which can be quantified by CCT using the Agatston calcium-scoring method, is a critical marker of valvular disease severity.[87]

Flow changes. Aging-associated valvular thickening and fusion can result in flow changes across the valves. More recently, aortic flow changes have been shown to be associated with aging and exercise capacity.[88] Importantly, flow changes, namely, increased turbulent oscillatory flow at the level of the valve leaflet, are associated with increased inflammation and interstitial cell activation, resulting in calcification.[29] Flow eccentricity in the ascending aorta, measured by flow displacement during systole, increases with ageing ($R = 0.69$, $P < 0.001$).[88] Moreover, increasing flow displacement in the ascending aorta is also independently associated with decreasing peak oxygen consumption ($R = -0.302$, $P < 0.0001$), as it results in more turbulent flow, which leads to energy loss, making the cardiovascular system even more ineffective.

TABLE 3 Multimodality Imaging in the Context of Vascular Aging

	Ultrasound	CCT	CMR	Nuclear
Structural changes with aging				
Calcification	++	+++	–	–
Plaque composition	+	+++	–	++
Plaque inflammation	–	+	–	+++
Geometric features associated with aging				
Arterial/aortic diameter or area	++	+++	+++	–
Carotid intima-media	++	+++	+	–
Plaque geometry	++	+++	–	–
Functional features associated with aging				
Vascular compliance				
Pulse-wave velocity	+++	–	+++	–
Aortic distensibility	+	++	+++	–
Vascular conduit function	++	–	+++	–

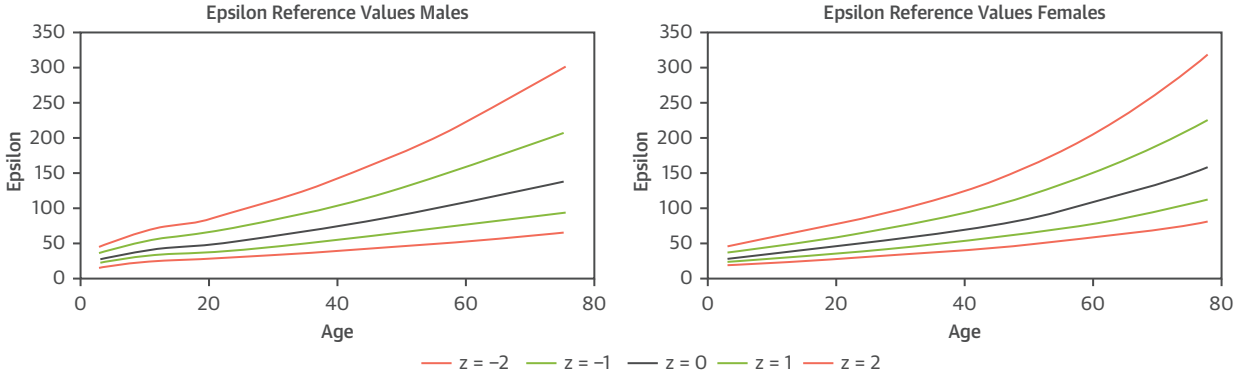
CCT = cardiac computed tomography; CMR = cardiac magnetic resonance.

Valvular stenosis. Valvular stenosis is the result of progressive valvular thickening and calcification. It results in obstruction to forward blood flow, which results in blood flow accelerating through the stenosis. Echocardiography,[89] CMR,[90] and CCT can evaluate the degree of valve opening and the pressure gradient across the valve, providing information about the severity of stenosis. Myocardial changes associated with increased loading conditions on the ventricle can also be evaluated by CMR tissue mapping techniques.[91]

Valvular regurgitation. With progressive fibrosis and loss of cellular density associated with aging, the valves become prone to tethering and rupture of leaflets. This results in age-related valvular incompetency associated with backward flow. Echocardiography and CMR remain the 2 main imaging modalities to assess the degree of valvular regurgitation. Recent studies have highlighted the emerging prognostic role of CMR quantification of valvular regurgitation and its associated physiological adverse LV adaptations.[92]

VASCULATURE. Multimodality imaging has a key role in characterizing vascular aging, showcasing the associated structural, geometric, and functional features as well as phenotypes that can be captured through imaging, which serve to enhance our understanding of the mechanisms underlying vascular aging (Table 3).

FIGURE 7 Carotid Arterial Stiffness Stratified by Age and Sex as Assessed Using Ultrasound Wall Tracking



This figure shows the impact of age on carotid arterial stiffness (measured as Peterson's elastic modulus) estimated by automated tracking of the media-adventitia boundary on ultrasound. Colors reflect the median value (black), upper and lower limited (*z*-scores of 1 and 2, green and red). Carotid epsilon is displayed as median value ± *z*-score separately for men and women. Reproduced with permission from Uejima et al,[96] licensed under CC BY 4.0.

With age, the arteries become stiffer because of the breakdown of elastin and the accumulation of collagen in the arterial walls.[93,94] A plethora of measurements have been used to assess large artery stiffness, driven in part by a huge variety of devices.[95] The fact that none has reached routine clinical practice attests to the underlying technical challenges of this measurement, not the least being that stiffness is influenced by arterial pressure. Imaging techniques are a viable alternative to sensors and cuff-based methods, which can be awkward to apply. In general, the imaging methods (mainly CMR but also ultrasound) may measure the aortic or carotid-femoral pulse wave. Central and peripheral artery measurements may be obtained with deformation imaging arising from the arterial pulse wave, or shear-wave elastography from intrinsic or extrinsic stimuli. These parameters are not necessarily concordant; for example, the ability of shear-wave imaging to be obtained over brief time intervals means that it can be calculated during 1 phase of the cardiac cycle (eg, diastole), whereas measures obtained from distensibility use the entire cycle (and might, for example, be corrected for pulse pressure). **Figure 7** shows the impact of age on carotid arterial stiffness (measured as Peterson's elastic modulus) estimated by automated tracking of the media-adventitia boundary on ultrasound.[96] The median measurement increased 2.2-fold in men and 2.5-fold in women between the third and seventh decades, with more than double this increment in the upper 5% of the population. Similar changes are recorded for beta stiffness index, with lesser changes (1.5-fold) for pulse-wave velocity.

The intimal and medial layers of the arteries thicken with increasing age, a process accelerated by hypertension and atherosclerosis. Vascular wall thickening can be quantified using vascular ultrasound, particularly by carotid artery intima-media thickness.[97] Advancing age is associated with an increase in plaque burden and alterations in plaque characteristics such as more calcific plaques and negative remodeling. Changes of the plaque characteristics, vulnerability, and atheroma burden may be visualized on CCT and intravascular imaging techniques such as intravascular ultrasound and optical coherence tomography.[98]

Calcification is a process through which calcium deposits form in the arterial walls, contributing to arterial stiffening. It is exacerbated by age.[99,100] The amount of calcium in the coronary arteries, as measured by the coronary artery calcium score, is strongly linked to the amount of plaque present.[101] Higher scores indicate a greater amount of plaque, which in turn is associated with a heightened risk for negative cardiovascular events. Indeed, calcium score may be used to predict vascular age in at risk populations.[102]

ELECTROCARDIOGRAPHY. Progressive age-related conduction changes may be captured on electrocardiographic (ECG) traces and have been described for many decades. The frequency of these changes differs across sexes and ethnic groups.[103,104] More recently, there has been growing interest in applying artificial intelligence (AI) methods to detect subtle ECG changes relating to aging, which could be used as adjuncts to cardiac imaging. Deep learning models have been successfully trained to estimate chronological age from an ECG trace, and the difference between the AI-assisted electrocardiographically predicted age and chronological age ("delta age") appears to be a good marker of biological aging.[105-107] AI-assisted Electrocardiographically predicted age exceeding chronological age is associated with low LVEF, heart failure, hypertension, coronary artery disease, stroke, atrial fibrillation, and mortality.[105-107] These metrics may be complementary to, and could be combined with, cardiac imaging, to estimate biological age.

THE ROLE OF "BIG DATA" IN UNDERSTANDING AGING

BIG DATA APPROACHES TO BIOLOGICAL HEART AGE ESTIMATION. The past decades have witnessed an increasingly availability of large-scale biobanks with deep phenotyping, including high-throughput molecular profiling, multiorgan imaging, and health record linkage driving "big data" research in health care. Among these, biological age estimation has emerged as an area of growing interest.

Biological age can be estimated using biomarkers of organ-level or whole-body structure and function, including cellular, imaging, physiological, and biochemical metrics, with their individual strengths and limitations.[108] Most commonly, biological age is estimated using regression or machine learning models that take biomarkers as input and chronological age as the output variable. The "age gap" (or delta) is then calculated by subtracting chronological from the model estimated biological age. A positive age gap thus represents a biological age that is greater than the chronological age and indicates unhealthy aging. The age gap metric may then be used as a target phenotype in genome-wide or phenome-wide association studies to reveal factors that influence greater (or reduced) biological aging.

Any biomarker (or combination of biomarkers) with enough volume and complexity could be used

to train age estimation models. Within cardiology, large-scale cardiovascular imaging and ECG data have been used as predictors for biological age estimation models.

In a study of almost 40,000 UK Biobank participants, Shah et al[109] used machine learning methods to estimate biological heart age with CMR-derived measures of cardiovascular structure and function and ECG traits used as model predictors. The Evaluation of associations with the age gap metric derived from this model revealed environmental and genetic exposures related to greater biological heart aging.

Similar models have been developed using ECG data alone, and indeed heart age gap derived from ECG-based heart age estimation models has demonstrated significant associations with greater CVD risk.[110]

Others have used CMR[111] and carotid ultrasound[112] images (rather than derived phenotypes) as model input to estimate biological heart age and used attrition maps to understand differential aging patterns across cardiac structures informing the model output. The heart and vascular age gap calculated from these models has similarly been used to evaluate genetic and nongenetic correlates of biological age.

Biological heart age may also be estimated using novel imaging markers. CMR radiomics represents an image analysis method that may be used to derive highly detailed quantitative information about ventricular and myocardial geometry and myocardial tissue character using pixel-level information from existing CMR images.[113] Growing evidence has highlighted the validity and potential clinical utility of CMR radiomics for superior disease detection and outcome prediction.[114-116] Previous work has demonstrated distinct alteration in CMR radiomics features with age. Among healthy individuals, increasing age has been linked with radiomics features indicating (on average) smaller and less spherical LV and greater variation in myocardial signal intensities.[117] Biological heart age estimates developed using CMR radiomics have proved useful in detecting environmental exposures that drive premature biological heart aging, with obesity and adverse serum lipids emerging as dominant factors.[118,119]

DNA METHYLATION. Similarly to heart age, genome-wide DNA methylation profiles can be leveraged for constructing epigenetic clocks using machine learning.[120] Increased epigenetic age acceleration is associated with disorders such as cancers, dementia, CVD, and mortality.[121] Epigenetic age acceleration has been associated with recognized components of cardiovascular health such as diet[122,123] and body mass index,[123,124] while lower epigenetic age acceleration is associated with better cardiovascular health[125,126] and reduced cardiovascular mortality.[127,128] The presence and extent of subclinical atherosclerosis (quantified through different imaging techniques) were found to be associated with a significant acceleration of epigenetic age in healthy subjects.[129]

TELOMERE LENGTH. Telomeres are nucleoprotein complexes that ensure chromosomal integrity during subsequent cell divisions. Somatic cell divisions lead to telomere shortening with increasing age, inducing cellular senescence. Leukocyte telomere length (LTL) is an indicator of biological age that correlates with telomere length in other tissues.[130] Age-related LTL shortening is influenced by genetics[131] and the environment.[7,132] Shorter LTL has been associated with increased risk for coronary artery disease[133-135] and heart failure[136] and causally associated with atherogenesis[137] and adverse LV remodeling.[26]

CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL. Recent analyses of population-based next-generation sequencing data have revealed that about 10% of individuals >70 years carry subclinical preleukemic mutations in circulating blood cells.[138,139] This condition, termed clonal hematopoiesis of indeterminate potential (CHIP), is often driven by genes involved in epigenetic regulation, including DNA methyltransferase 3 alpha, Tet methylcytosine dioxygenase 2, and ASXL transcriptional regulator 1. Observational and experimental data support CHIP as an independent aging-related risk factor for atherosclerotic CVDs[140-144] and heart failure,[145,146] with varying risks and mechanisms across driver genes.[140,145] Mounting evidence implicates cardiac fibrosis and inflammatory dysregulation in the cardiovascular risk associated with CHIP.[141,144,147]

PROTEOMICS AND OMICS. Proteins and metabolites play a crucial role in translating genetic information into observable phenotypes.[148] The aging proteome is influenced by various factors, including protein translation, post-translational modifications, aggregation, and degradation. Key protein pathways (eg, insulin-like growth factor regulation or hypoxia-inducible factor signaling) show specific patterns with aging and therefore could serve as markers to track age-related changes.[148] Although some identified pathways might have important implications to heart aging, CVD-related proteomic signatures are insufficiently described.[149,150] By pinpointing specific molecular changes, proteomics is facilitating the

HIGHLIGHTS

- Biological cardiovascular aging has a variable relationship to chronological age.
- The aging heart may be captured using imaging and other non-invasive techniques.
- Cardiovascular biomarkers may be used to estimate biological heart age.
- Further research is needed to determine the utility of biological age estimates.

development of targeted therapies, such as senolytics, whose aim is to selectively eliminate senescent cells and extend the healthy life span.[151] Advances in amyloid typing and subsequent improvements in therapy are examples of how proteomics can enable targeted therapeutics in the future.[152]

CONCLUSIONS AND FUTURE WORK

Promotion of healthy cardiovascular aging is a global public health priority. Biological aging contributes to physiological decline across multiple organ systems leading to functional decline and predisposition to age-related illnesses. The distinct manifestations of cardiovascular aging may be captured using imaging and other noninvasive techniques. These methods can be used to better understand trends of healthy biological aging and to detect deviations from this trend. Cardiovascular imaging and other derived biomarkers may be used in mathematical methods to estimate biological heart age. Using these models genetic and environmental determinants of aging may be investigated and phenotypic alterations associated with aging may be deciphered. The estimates produced by these methods vary by the populations on which the models are trained, the predictor variables used, and the precise modeling methods. The development of standards for methods and reporting are important next steps to ensure cross-comparability and maintenance of research quality in this field. The clinical utility of "delta age" metrics (beyond research tools) is not established, and future work will need to address the incremental prognostic value provided by biological age estimates over chronological age and easily measured demographic information. The biological age estimation field is expected to be an area of high activity in coming years because of greater availability of suitable data sets and computing means for analysis and the need to better understand aging processes. Multimodality cardiovascular imaging will play a pivotal role in advancing knowledge about the form and function of the aging heart and in development of strategies to promote healthy cardiovascular aging at the population and individual levels.

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