Heart failure (HF) is a clinical syndrome that usually develops in the elderly. Complex interactions of the cardiovascular aging process with risk factors (obesity, hypertension, and atherosclerosis), comorbidities (anemia, chronic kidney disease, diabetes, and so on), and disease modifiers (sex, genes, others) contribute to the development of HF phenotype and outcome. A conglomerate of cellular and molecular mechanisms underlies the effects of aging on cardiovascular function, the most important being excessive oxidative stress and chronic low-grade inflammation superimposed on the limited cardiac regeneration capacity. Notably, a sizeable percentage of elderly HF patients have cardiac amyloidosis, an HF precipitator. This review summarizes the current published data on the mechanisms of cardiovascular aging as they contribute to the development of HF phenotype and outcome. (J Am Coll Cardiol 2019;74:804–13)

© 2019 by the American College of Cardiology Foundation.

Heart failure (HF) prevalence increases dramatically in the elderly. In the Rochester Epidemiologic Project in Olmsted County, the overall prevalence of HF was 2.2% and increased with age, reaching 8.4% in those age ≥75 years compared with 0.7% in those 45 to 54 years of age (1). Likewise, HF incidence increases with age. In the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) study, HF incidence was low before the age of 60 years and increased markedly after 60 years, whereby the lifetime risk for developing HF was approximately 38% at 90 years of age (2).

This review summarizes the current published data on the mechanisms of cardiovascular aging as they contribute to the development of HF phenotype and outcome.

MECHANISMS OF CARDIOVASCULAR AGING

Age is a major determinant of the risk for cardiovascular disease (3). The major implicated processes are excessive oxidative stress and chronic low-grade inflammation superimposed on the limited cardiac regeneration capacity (4). Other fundamental mechanisms of biological aging comprise cellular senescence, reduced stress resistance, genomic instability, telomere attrition, reduced proteostasis, stem cell dysfunction, and/or epigenetic modifications, along with dysbiosis of the gut and/or oral microbiomes (5).

OXIDATIVE STRESS. Mitochondria, the major intracellular source of reactive oxygen species, are considered central controllers of the aging process (Figure 1) (6).

From the Department of Cardiology, Larissa University General Hospital, Larissa, Greece; and the Department of Medicine, University of Mississippi, Jackson, Mississippi. Dr. Triposkiadis has received research support and honoraria from Amgen, Bayer, Boehringer Ingelheim, Elpen, Lilly, Menarini, Merck, Novartis, Sanofi, Servier, Vianex, and WinMedica. Dr. Butler has received research support from the National Institutes of Health, Patient Centered Outcomes Research Institute, and the European Union; has served as a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, BerlinCures, Boehringer Ingelheim, Bristol-Myers Squibb, Cardiocell, Corvidia, CVRx, C3 Pharmaceutical, Innolife, Janssen, Lantheus, LinaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, SC Pharma, StealthPeptide, V-Wave Limited, Vifor, and ZS Pharma; and has participated in educational programs for Medscape. Dr. Xanthopoulos has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received April 23, 2019; revised manuscript received June 26, 2019, accepted June 27, 2019.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.06.053
HIGHLIGHTS

- Cardiovascular aging leads to a progressive decline in structure and function.
- Mitochondria are central controllers of the aging process.
- Risk factors/comorbidities on top of cardiovascular aging promote HF.
- Lifestyle modifications reduce risk and should be implemented from childhood.

Aged cardiomyocytes show abnormalities in mitochondrial structure (enlarged organelles, matrix derangement, and loss of cristae) and increased generation of free radicals, which are considered a major driver of cardiomyocyte senescence (7). Mitochondrial dysfunction is also associated with disturbed calcium signaling due to changes in the type 2 ryanodine receptor (RyR2) and the sarcoplasmic reticularum Ca2+ ATPase pump (SERCA) (8). Moreover, aged cardiomyocytes cannot dilute damaged mitochondria by proliferation because most reside in a post-mitotic state. At the same time, their catabolic defensive mechanisms, namely autophagic and proteasomal degradations, decline with age (9). In this context, the formation of covalent cross-linked protein aggregates, like lipofuscin, is of special importance as their abundance in aged cells has detrimental effects (10).

INFLAMMATION. A chronic pro-inflammatory status is a characteristic feature of aging. This chronic low-grade inflammation occurring in the absence of overt infection has been defined as “inflammaging” and represents a significant risk factor for morbidity and mortality in the elderly (11). Potential mechanisms of inflammaging include genetic susceptibility, central obesity, increased gut permeability, changes to microbiota composition, cellular senescence, NLRP3 inflammasome activation, oxidative stress caused by dysfunctional mitochondria, chronic infections, and immune cell dysregulation (12).

LIMITED MYOCARDIAL REGENERATION. The heart muscle in adult mammals has limited endogenous regenerative capacity in response to injury (13).

Age-dependent renewal of cardiomyocytes with the highest turnover occurs during the first 2 decades of life, corresponding to rates of ~1%/year at the age of 20 years, declining to lower than 0.5%/year in elderly individuals (14). In contrast, there is a high turnover rate of endothelial cells throughout life (>15%/year) and more limited renewal of mesenchymal cells (<4%/year in adulthood) (15).

Progenitor cells play an important role in vascular repair and regeneration. In 642 individuals (mean age 48 years, 69% women, 23% black) who were free from cardiovascular disease, Topel et al. (16) observed an age-related decline in circulating progenitor cells in both sexes (Figure 2). The regulation of cardiovascular regeneration is mediated by miRNAs (17).

AGING HEART

MORPHOLOGY AND FUNCTION. In healthy individuals, aging results in an increase in the incidence of left ventricular (LV) hypertrophy, decline in LV diastolic function, left atrial (LA) dilatation, preservation of left ventricular ejection fraction (LVEF), decline in exercise capacity, and an increase in the prevalence of atrial fibrillation (AF).

Cheng et al. (18) used cardiac magnetic resonance imaging (CMR) to examine LV structure and function in 5,004 participants without cardiovascular disease. The mass-to-volume ratio markedly increased with age (+5 mg/ml/year). Age was also associated with a significant fall in stroke volume (~0.4 ml/year), along with strain patterns reflecting systolic as well as diastolic myocardial dysfunction, despite a modestly enhanced LVEF (+0.1%/year) (18). Nayor et al. (19) estimated age-specific reference limits for echocardiographic measures of diastolic dysfunction in healthy individuals (n = 2,355, mean age 44 years, 66% women). Diastolic dysfunction was rare until 50 years of age, but thereafter, its prevalence and severity rose steeply. Over one-half of the participants had diastolic dysfunction by 70 to <80 years of age, and more than two-thirds did after 80 years of age (19).

Another characteristic of cardiovascular aging is the reduction in maximal heart rate, which is due to decreased intrinsic heart rate and chronotrophic responsiveness to β-adrenergic stimulation (20). In contrast, the activity of the sympathetic nervous system increases with aging (4).

The reduction in maximal heart rate together with the reduction in LV stroke volume despite the higher LV filling pressure due to the decreased LV relaxation and compliance (21), result in aging induced diminished maximal cardiac output, culminating in a compromised cardiac reserve capacity (22). An aging myocardium also possesses significant intrinsic electrophysiological alterations that are modulated by the
cardiac autonomic nervous system and predispose the elderly patient to arrhythmic risk (23).

Finally, degenerative abnormalities associated with severe aortic stenosis and mitral and tricuspid regurgitation are found in approximately 10% of the population aged ≥75 years (24). Aortic stenosis is partly due to active processes common with those of atherosclerotic disease, whereas mitral regurgitation is usually secondary.

LA volume and function are affected by age. LA maximal and minimal volume increase, especially in individuals who have cardiovascular risk factors (25).

Evin et al. (26) studied LA function in 94 healthy adults (age 41 ± 14 years, 47 women) with CMR and Doppler echocardiography. Longitudinal strain and radial motion fraction decreased with aging in both the reservoir and conduit phases, but remained unchanged for LA contraction (26). LA dilation and mechanical dysfunction are major risk factors for the development of AF (27).

The right ventricle (RV) and the pulmonary vascular system undergo significant changes with aging. Pulmonary artery pressure and vascular resistance mildly increase with normal aging, likely secondary to an increase in pulmonary arterial stiffness. RV ejection fraction remains relatively well preserved with aging, as does LVEF. RV diastolic dysfunction develops with time (28). Changes in RV systolic reserve with exercise parallel the decline seen in LV systolic reserve. Finally, the geometry of the RV inflow tract changes with age (29).

The right atrial (RA) volume increases with age, and RA flow disturbances are significantly more frequent in the elderly (29).

MYOCARDIAL FIBROSIS. Aging is associated with the development of myocardial fibrosis (Figure 3) (30). Fibrotic tissue is stiffer and less compliant, resulting in subsequent cardiac dysfunction and increasing the risk of HF (31).

The mechanisms inducing fibrogenic signals are diverse. Activation of neurohumoral pathways stimulates fibroblasts, both directly and through effects on immune cell populations (32). Angiotensin II acts as a pro-inflammatory molecule and pro-fibrotic agent. Binding of angiotensin II to its receptors (in particular, AT1) is followed by intracellular free radical generation that contributes to tissue damage by promoting mitochondrial dysfunction (33). Cytokines and growth factors are secreted in the cardiac interstitium, whereas fibrogenic mediators and matricellular proteins bind to cell surface receptors in fibroblasts and transduce intracellular signaling cascades that regulate genes involved in synthesis, processing, and metabolism of the extracellular matrix. Endogenous pathways involved in negative regulation of fibrosis are critical for cardiac repair and may protect the myocardium from excessive fibrogenic responses.

CARDIAC AMYLOIDOSIS. Autopsy studies demonstrated that approximately 25% of all adults >85 years of age have acquired wild-type variant (ATTRwt) cardiac deposits (34), with 5% to 10% manifesting the clinical phenotype of cardiac ATTRwt (35). Gonzalez-Lopez et al. (36) demonstrated in a prospective study, including patients ≥60 years of age admitted with
HF, LVEF ≥50%, and LV hypertrophy (≥12 mm), that 13% of patients had ATTRwt cardiac amyloid.

The deposition of amyloid fibrils in the extracellular matrix increases ventricular wall thickness and myocardial stiffness (37). As these morphological patterns are nonspecific, it seems likely that cardiac amyloidosis is much more common than currently appreciated (38).

The underlying mechanisms leading to the development of cardiac ATTRwt are still being debated, but aging may destabilize transthyretin by post-transcriptional biochemical alterations in the protein per se or its chaperones (39,40).

**AGING VASCULATURE**

Aging is characterized by progressive fragmentation and eventually break down of the elastic components of the aortic media, which are partially replaced by highly cross-linked collagen (41) leading to stiffening, dilation, and elongation of the aorta (Figure 4) (42). A general increase in intimal-medial thickness of medium-sized arteries is also observed (43). A major underlying mechanism is endothelial dysfunction due to high oxidative stress and low-grade inflammation (44).

The aorta plays a pivotal role in the optimization of vascular-ventricular coupling. Moreover, it acts as the primary cushion in buffering and smoothing the pulsatile pressure blood flow as it travels from the heart to the periphery (41).

In the stiffened aorta, systolic pressure and LV afterload rise, leading to LV hypertrophy and increased myocardial oxygen demand, whereas aortic diastolic pressure decreases, resulting in perfusion-metabolism mismatch and myocardial ischemia.
Coronary endothelial dysfunction may also contribute to the development of myocardial ischemia (45). Moreover, a stiff aorta also transmits greater pulsatile energy to the microcirculation, which may lead to peripheral organ damage (46). The sexes differ in large artery biomechanical properties throughout the lifespan, with females displaying higher stiffness than males during the prepubertal years and a dramatic increase after menopause (47). Aortic hemodynamics also depend on age. Garcia et al. (48) studied 98 healthy subjects (age 9 to 78 years, 41 women) with 4-dimensional flow CMR for the assessment of 3-dimensional blood flow in the thoracic aorta. Aortic peak velocity measures in young individuals (age 21 to 39 years) were 25% lower than those of older individuals (age >60 years).

Increased aortic stiffness contributes to the development of isolated systolic hypertension, which is extremely common in the elderly (49).

**HF RISK FACTORS**

Risk factors always precede the development of HF and are associated with an increased HF incidence.

**HYPERTENSION.** The lifetime risk of hypertension approaches 90% for middle-aged, normotensive adults (50). The traditional concept is that cardiac...
remodeling in hypertension is due to pressure overload leading to concentric LV hypertrophy (51). When pressure overload is sustained, HF with near-normal/normal LVEF develops. The end stage of hypertensive heart disease consists of eccentric hypertrophy with reduced LVEF. However, although increased blood pressure is considered the major determinant of LV structural alterations, other factors (ethnicity, sex, salt intake, obesity, diabetes mellitus, neurohumoral activity, genes) may influence LV mass and geometry (52). As a result, concentric hypertrophy is not the only geometric pattern, and eccentric hypertrophy may be seen in hypertensive subjects.

**ISCHEMIC HEART DISEASE.** Autopsy studies indicate that obstructive coronary artery disease is present in approximately 60% of individuals >60 years (53). Older patients with coronary artery disease tend to
have more severe and more diffuse coronary atherosclerosis than younger adults.

LV remodeling in coronary artery disease usually occurs after a myocardial infarction (MI). Gaudron et al. (54) evaluated LV volumes in 70 patients after their first myocardial infarction using gated single-photon emission computed tomography. Almost 26% of patients developed limited LV dilation within 4 weeks after first myocardial infarction, whereas 20% had progressive structural LV dilation (54).

LV remodeling involves a wound-healing orchestra involving a variety of cell types. For wound healing to be optimal, these cells all need to come in at the right time, be activated at the right time in the right amount, and know when to exit at the right time. When this occurs, a new homeostasis is obtained within the infarct, such that infarct scar size and quality are enough to maintain LV size and shape. However, miscommunication often occurs, and adverse remodeling can progress to HF (55).
OBESITY. Approximately 35% of adults in the United States age 65 years and older between 2007 and 2010 were obese as defined by body mass index (56).

Obesity (especially visceral adiposity) can be associated with HF with low LVEF, HF with near normal/normal LVEF, and high-output HF. All 3 types are characterized by an excessive secretion of aldosterone and sodium retention. In addition, obesity is accompanied by increased signaling through the leptin receptor, which can promote activation of both the sympathetic nervous system and the renin-angiotensin system and can directly stimulate the secretion of aldosterone (57).

LIFESTYLE INFLUENCES. Low-active and sedentary behavior augment whereas physical activity and exercise attenuate cardiovascular function decline with aging (58). Dietary patterns affect arterial aging. In addition, some individual micronutrients have powerful effects on cardiovascular aging. For example, a high sodium intake is associated with endothelial dysfunction and increased arterial stiffness (59). Alcohol can influence arterial properties beneficially when consumed at low to moderate doses, or unfavorably at high doses through mechanisms related to nitric oxide and endothelin 1 secretion, as well oxidative stress and inflammation (60). Smoking accelerates the aging process, both directly through excessive free radical formation and indirectly by favoring the appearance of various pathologies (61).

COMORBIDITIES

Comorbidities may precede or develop after HF and usually coexist with HF in groups of 2 or more (multimorbidity).

ATRIAL FIBRILLATION. AF promotes HF and vice versa in the elderly. Santhanakrishnan et al. (62) studied Framingham Heart Study participants with new-onset AF or HF. Among 1,737 individuals with new AF (mean age 75 ± 12 years; 48% women), more than one-third (37%) had HF. Conversely, among 1,166 individuals with new HF (mean age 79 ± 11 years; 53% women), more than one-half (57%) had AF (62).

Current worldwide epidemiological data on AF confirm the emergence of this condition as a global epidemic, with higher rates observed in older age groups (63). Aging-related atrial remodeling with fibrosis, dilation, and mitochondrial DNA mutations predispose elderly patients to AF (64).

NONCARDIOVASCULAR COMORBIDITIES. Noncardiovascular comorbidities (anemia, chronic kidney disease, diabetes mellitus, depression, pulmonary diseases, sleep disordered breathing, and others) are common and increase morbidity and mortality risk in HF (65). The results of the studies investigating the relationship between aging and comorbidity burden depend on the characteristics of the trial population. Studies including chronic stable HF patients suggest that those with a greater burden of noncardiovascular comorbidities are older (66), whereas studies including hospitalized HF patients that they are younger (67).

AGING AND HF

PHENOTYPE DETERMINANTS. Each HF phenotype is determined by the patient’s risk factors, comorbidities, and disease modifiers superimposed on the cardiovascular aging process, which acts as a scaffold (68).

Elderly women with HF are more likely than men to have HF associated with concentric remodeling/hypertrophy and near-normal/normal LVEF. This has been attributed to sex-biased miRNAs, which are regulated by E2 or are expressed from loci on the X-chromosome due to incomplete X-chromosome inactivation (69). Interestingly, whereas E2-induced miRNAs predominantly appear to serve protective functions, many X-linked miRNAs have been found to challenge microvascular and myocardial integrity. Thus, menopausal E2 deficiency, resulting in protective miRNA loss and the augmentation of X-linked miRNA expression, may contribute to the female-specific cardiovascular etiology in HF with near normal/normal LVEF.

In contrast to women, men with HF are relatively younger and more likely to have eccentric hypertrophy with low LVEF, frequently associated with obstructive coronary artery disease. Female sex affects favorably outcomes of HF (70,71).

PREVENTIVE STRATEGIES

Embracing a healthy lifestyle, especially starting in childhood, has a powerful effect in reducing the risk of developing age-related chronic diseases (72). The traditional Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets appear to be protective. Moreover, calorie restriction with adequate intake of specific nutrients, in conjunction with regular exercise, stress reduction, and smoking avoidance, is a powerful tool to slow cardiovascular aging. However, to achieve the extraordinarily extended health of centenarians, the additional use of drugs will most likely be necessary (73).
CONCLUSIONS

Complex interactions among cardiovascular risk factors, comorbidities, and disease modifiers superimposed on the cardiovascular aging process contribute to HF development and outcome (Central Illustration). Cardiovascular aging research has undergone unprecedented advances in recent years, leading to opportunities for innovation. Novel insights indicate that the cardiac vulnerability of aging is predominantly driven by nonadaptive mechanisms and the health dimensions of the morbidity process is predominantly driven by nonadaptive mechanisms and the health dimensions of the morbidity process.

REFERENCES

33. Mohammed SF, Mirzoyez SA, Edwards WD, et al. Left ventricular amyloid deposition in...


37. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol 2010;7: 398–408.


KEYWORDS: aging, amyloidosis, comorbidities, heart failure, risk factors