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Review

Healthy aging and myocardium: A complicated process with various effects in cardiac structure and physiology

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ABSTRACT

It is known that there is an ongoing increase in life expectancy worldwide, especially in the population older than 65 years of age. Cardiac aging is characterized by a series of complex pathophysiological changes affecting myocardium at structural, cellular, molecular and functional levels. These changes make the aged myocardium more susceptible to stress, leading to a high prevalence of cardiovascular diseases (heart failure, atrial fibrillation, left ventricular hypertrophy, coronary artery disease) in the elderly population. The aging process is genetically programmed but modified by environmental influences, so that the rate of aging can vary widely among people. We summarized the entire data concerning all the multifactorial changes in aged myocardium and highlighting the recent evidence for the pathophysiological basis of cardiac aging. Keeping an eye on the clinical side, this review will explore the potential implications of the age-related changes in the clinical management and on novel therapeutic strategies potentially deriving from the scientific knowledge currently acquired on cardiac aging process.

Time modifies many biologic processes. Aging is characterized by progressive and broadly predictable myocardial changes that complicate the maintenance of homeostasis. Cardiac homeostenosis, an age-associated physiologic change, refers to the concept that, from maturity to senescence, diminishing myocardial reserves are available to meet challenges to homeostasis. This concept was first recognized by Walter Cannon in the 1940s [1]. Cardiac homeostenosis leads to increased vulnerability to cardiovascular disease that occurs with aging. These age-associated changes must be construed as specific risk factors for cardiovascular diseases, thus the knowledge of the physiology of the effect of normal aging on the cardiac structure and function is essential for the fundamental understanding of the pathophysiology of cardiovascular diseases (CVD) in the elderly.

The majority of definitions of aging are based on calendar age. Gerontologists distinguish between 3 subgroups: younger old people (60–74 years), older people (75–85 years) and very old people (>85 years) [2]. The World Health Organization defines senility as the age of >60 years (http://www.who.int/).

According to epidemiological data, the proportion of the elderly population worldwide is increasing. It is estimated that in the United States of America (USA) the population of people who are aged above 65 years is expected to increase from 35 million in 2000 to 87 million in 2030, a percentage of 147%. At the same time, the population over the age of 85 years is expected to increase by a percentage of 389% [1]. Moreover, the incidence of CVD increases linearly with age. Over 80% of cases of coronary artery disease (CAD) and more than 75% of those of congestive heart failure (CHF) are observed in elderly patients [3]. The incidence of CVD, including CAD, CHF and stroke, increases from 4–10/1,000 person-years in adults aged 45–54 years to 65–75/1,000 person-years in those older than 85 [4].

There is a continuum of expression of cardiac structural, functional, cellular and molecular alterations that occur with age in healthy humans and these age-associated cardiac changes seem to have relevance to left ventricular hypertrophy (LVH), chronic heart failure, and atrial fibrillation (AF) that are seen with increasing age (Fig. 1).

1. Structural changes

1.1. Remodeling of left ventricle

Cross-sectional studies of subjects without hypertension or another cause of afterload increase indicate that left ventricular (LV) wall thickness, measured via M-mode echocardiography, increases progressively with age in both sexes [5]. Ventricular cardiomyocytes hypertrophy, in part as a response to the increased afterload produced by large artery stiffening [6].

Moreover, partly as a result of the decrease in long-axis dimension and partly as a result of a rightward shift of the dilated ascending aorta during normal aging, the basal ventricular septum bends leftward, bulging into the left ventricular outflow tract [7]. This alteration in shape yields a curved ventricular septum which has been termed the "sigmoid septum" by Goor and colleagues [8]. As a consequence, the basal ventricular septum bulges into the left ventricular outflow tract and may mimic asymmetric septal hypertrophy of hypertrophic cardiomyopathy [7]. Moreover, the left atrium enlarges and left atrial volume,

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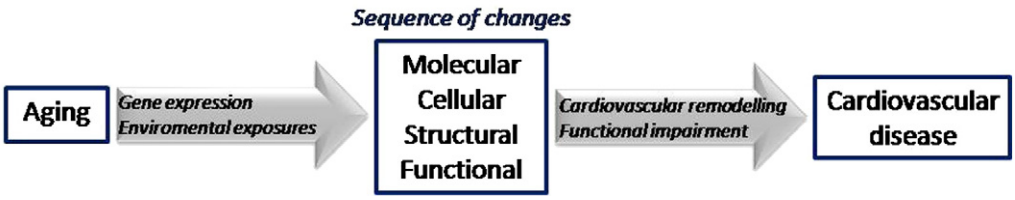

Fig. 1. The pathophysiological pathway leading in cardiovascular disease in aged myocardium.

corrected for body size, increases roughly 50% from the third decade to the eighth [9], thereby explaining in part the high prevalence of atrial fibrillation in the elderly population.

Similar anatomical changes are observed in the right side of the heart, although they are not as prominent as in the left side [10]. In The Multi-Ethnic Study of Atherosclerosis-Right Ventricle Study there was an ≈5% decrease in right ventricular (RV) mass for every decade increase in age, although men had statistically significantly larger age-related decrements in RV mass (1.0 g per decade) than women did (0.8 g per decade) even after adjustment for covariates [11]. Moreover, age-related reductions in RV end systolic and end diastolic volumes (ESV and EDV), assessed by magnetic resonance have been reported [11,12].

1.2. Valvular changes

1.2.1. Aortic valve

Calcific or degenerative aortic valve disease is considered the most common valvular lesion encountered among elderly patients [13]. Calcific aortic valve disease is a slowly progressive disorder with a disease continuum that ranges from mild valve thickening without obstruction of blood flow, termed aortic sclerosis, to severe calcification with impaired leaflet motion, or aortic stenosis [13]. This process is thought to be "degenerative" because of time-dependent wear-and-tear of the leaflets with passive calcium deposition [14]. The prevalence of calcific aortic stenosis increases with age, being present in 2% to 4% of adults over age 65 years [15].

Aortic sclerosis is common, present in 25% of people 65 to 74 years of age and in 48% of people older than 84 years [14]. In the Cardiovascular Health Study, 29% of the 5621 subjects aged over 65 had aortic sclerosis on echocardiography [15]. A similar study looking at an older population (mean age 82 years) found a prevalence of 42% [15]. However, the prevalence rises further in a higher cardiovascular risk population [15]. Aortic sclerosis is associated with an increase of approximately 50% in the risk of death from cardiovascular causes and the risk of myocardial infarction [15]. The overlap in the clinical factors associated with calcific valve disease and atherosclerosis and the correlation between the severity of coronary artery and aortic valve calcification provide further support for a shared disease process.

Lambl's excrescences appear to be wear-and-tear lesions that originate in the endothelium of the contact margins of a valve, commonly the aortic valve [16]. However, they may occasionally be found in much younger patients, including children. These excrescences have been observed on echocardiography (commonly in the transesophageal echocardiography), they are similar to papillary fibroelastoma neoplasms, but differ in size and location. In clinical practice, they can cause turbulence, and they are a site of relative stasis where thrombosis may occur and thus may provide a site for the development of infective endocarditis [16]. Additionally, coronary ostial obstruction and embolization of fragments or excrescences have occasionally been reported [16].

Furthermore, the prevalence of aortic regurgitation increases with age, as a result of calcification of the aortic cusps and annulus. In a prospective study it was shown that 16% of older people had moderate to severe aortic regurgitation [17].

1.2.2. Mitral valve

Mitral annular calcification (MAC) develops from progressive calcium deposition along and beneath the mitral valve annulus [18]. MAC is associated with atrial fibrillation, conduction system disease, atherosclerotic disease and adverse cardiovascular events, including stroke and mortality [19–23].

The prevalence of MAC increases with age [24–26]. In the multiethnic Northern Manhattan study cohort of 1955 subjects 40 years of age or older (mean age 68 years) without prior myocardial infarction or ischemic stroke, MAC was identified by two-dimensional echocardiography in 27% [19]. In two population-based studies with mean ages of 70 and 76 years, the prevalence of MAC was 14% (by M-mode echocardiography) and 42% (by two-dimensional echocardiography) [20,26].

Although MAC is usually unrelated to clinical symptoms, when mitral annular calcification is massive, it can lead to valvular dysfunction, typically resulting in complete heart block, mitral regurgitation, or less often, mitral stenosis. MAC may also become ulcerated and infected, giving rise to emboli, thus having a direct causative role in the pathophysiology of thromboembolism.

It has been described a type of normal aging-related changes of mitral valve in the elderly which may mimic the mitral valve prolapse pattern, the mitral valve leaflet "buckling" [7]. As left ventricular cavity size decreases with advancing age, the area containing the mitral leaflets and chordate tendineae is reduced. Thus, during ventricular systole the mitral leaflet "buckle" or protrude into the left atrium — a "leaflet-cavity disproportion" phenomenon [7]. This leaflet protrusion may mimic the mitral valve prolapse pattern. Echocardiographic distinction of the elderly normal buckling mitral valve from the abnormal prolapsed mitral valve can be made by observing thickened leaflets of the prolapsed valve compared to thinly appearing leaflets of the normal old-age mitral valve [7].

1.3. Conduction system

Loss of myocytes with age has been reported to occur in the sinoatrial (SA) node and more modest cellular loss at the atrioventricular node. This may underlie increased sensitivity of the older SA node to calcium channel blockers [27]. It has been reported that a reduction to less than 10% of cardiac pacemaker cells in respect to young adults results in the dysfunction of the sinoatrial node (SAN) with an increase in the nodal conduction time and a decrease in the intrinsic heart rate [28]. Heart rate is influenced not only by the loss of cells in the sinoatrial node (responsible for controlling heart rate) but also by structural changes in the heart, including fibrosis and hypertrophy, which slow propagation of action potential. Indeed, a significant decrease in the SA node's pacemaker cells, combined with the anatomical changes in SAN may result in the sick sinus syndrome, whose manifestations include bradycardia, sinus arrest, and sinus exit block [28,29]. The aforementioned structural changes exist to a smaller degree at the level of the atrioventricular node and bundle of His and to a greater degree within the bundle branches [27].

2. Cellular/histopathologic changes

Histopathologic changes in mouse hearts during cardiac senescence include subendocardial and interstitial fibrosis, hyaline cytoplasmic change, vacuolization of cytoplasm, variable and hypertrophic myocyte fiber size, collapse of sarcomeres and arteriolosclerosis [30]. Loss of myocytes with age has been reported to occur by apoptosis and necrosis or autophagy and the total number of cardiomyocytes may be reduced significantly in healthy human hearts. This process induces initially a compensatory remodeling characterized by the alterations of extracellular matrix (ECM) composition involving the synthesis of fibroblasts and the degradation of collagen through transforming growth factor-β (TGF-β) signaling. These alterations lead to the hypertrophy of the remaining cells and to pathologic remodeling, with consequent reactive fibrosis that increases cardiac stiffness and reduces the cardiac compliance [31]. Indeed, the disruption of ECM homeostasis is a key factor for the progression of cardiac dysfunction [32], including the pathogenesis of diastolic heart failure [33,34] and arrhythmias [35] in aging hearts. The cardiac myocyte-to-collagen ratio in the older heart either remains constant or increases, however, because of an increase in myocyte size [36]. Thus, a better understanding of the modulation of ECM regulatory components with aging will give rise to novel perspectives with therapeutic potential.

Moreover, senile or age-related transthyretin amyloid may be found in any chamber, the coronary arteries, the valves and the pericardium and it commonly deposits in a pericellular location around the myocytes. While present in around 80% of hearts in those over 80 years [37], it clinically affects around 25% of this age group [38]. In a small proportion of patients, the ventricular deposition is massive, resulting in infiltrative cardiomyopathy with heart failure [39,40]. The term senile cardiac amyloidosis is best reserved for these cases, since it is associated with a typical echocardiographic appearance and clinical course. A recent study of 102 patients with systemic senile amyloidosis showed that 96% were male, congestive heart failure was the presenting feature in 86% and the median age-adjusted survival (without disease-modifying therapy) was 4.6 years [41]. Moreover, there is evidence supporting association between atrial amyloidosis and atrial fibrillation [42].

3. Molecular changes

Extensive evidence demonstrates that age-related changes in the expression and function of various ion channels, receptors, enzymes and signaling pathways play a key role in the pathophysiological basis of the aged heart, affecting the mechanical and electrical properties of the myocardium.

3.1. Excitation–contraction coupling

A number of studies have investigated the impact of age on proteins involved in the excitation-contraction coupling pathways in the cardiac myocyte, that may provoke contractile decline and diastolic dysfunction in the aging heart [43,44,45]. Contraction is slowed in the aging heart, in part due to changes in myofilament proteins including a shift from α myosin heavy chain to β myosin heavy chain [45]. This results in a decrease in myosin ATPase activity in the aging heart [45]. An age-related decrease in the ability of sarco/endoplasmic reticulum Ca^{+2}-ATPase-2 (SERCA2a) to sequester Ca^{2+} in the sarcoplasmic reticulum (SR) may prolong the Ca^{2+} transient and slow contraction in the aging heart [40,45]. There is also an increase in the transcripts for the sodium–calcium exchanger, which serves to extrude calcium from the cell, further contributing to prolonged Ca^{+2} transient [45] and repolarization time with increased susceptibility to reentrant arrhythmias. These age-associated changes in calcium homeostasis have the potential to alter muscle relaxation mechanics, contributing to the reduction in early diastolic filling rate characterizing the aged myocardium.

3.2. Chronic dysfunction of neurohormonal signaling

Dysregulation of neurohormonal signaling pathways, including mechanistic target of rapamycin (mTOR), insulin-like growth factor-1 (IGF-1) and angiotensin II (Ang II) signaling, has been implicated in cardiac hypertrophy and aging. There is experimental evidence implicating the major role of mTOR signaling in cardiac aging process [46,47]. Although there is no evidence yet on the beneficial effects of genetic manipulation to decrease mTOR activity in the aging mammalian heart, inhibition of mTOR signaling by caloric restriction (CR) or rapamycin has been shown to protect against cardiac senescence (Fig. 2) [48]. Moreover, there is evidence supporting the controversial role of insulin/IGF1 signaling pathway on cardiac aging process [49,50,51] and further studies are required to clarify precisely the pathophysiological role of these factors on age-related myocardium dysfunction. Another significant neurohormonal alteration during cardiac senescence with the potential to affect not only the structure but also the function of myocardium, is the chronic activation of renin-angiotensin-aldosterone (RAAS) system. Although the mechanism of increased angiotensin-converting-enzyme (ACE) in the aged heart is not well understood, long-term inhibition with angiotensin receptor blockers or disruption of angiotensin receptor type I has been shown to extend lifespan and delay age-dependent cardiac pathology in animal models (Fig. 2) [52,53]. In addition to alterations in aforementioned neurohormonal factors, several lines of evidence have indicated the presence of age-related change in the adrenergic modulation, which has been explained by a mechanism called "β-adrenoceptor desensitization" [54]. It is a process characterized by β-adrenergic receptors (β-AR) molecular changes: phosphorylation of receptor structures enhanced by an agonist receptor bind state, that induces the reduction of receptors density and their internalization. This process is also well-described in the heart failure [55]. The age-induced "β-adrenoceptor desensitization" is responsible for the reduction in the autonomic modulation of the cardiac system, especially during physical exercise [56,57]. Moreover, another type of evidence for the diminished efficacy of synaptic adrenergic receptor signaling is that cardiovascular responses at rest to adrenergic agonist infusions decrease with age [36].

3.3. Reduced regenerative capacity of cardiac stem cells

Increasing evidence suggests that the regenerative capacity of cardiac stem cells declines with aging and that such declines may mediate the impaired myocardial repair in aged hearts. Cardiac stem cells in the aged heart may have impaired regenerative capacity, either by senescence intrinsic to the stem cells or by an extrinsic hostile microenvironment associated with advanced age [58,59]. Torella et al. showed that the percentage of cardiac stem cells that exhibited evidence of senescence, i.e., $p16^{ink4a}$ expression, telomere shortening, and apoptosis, was higher in older animals and the IGF-1 overexpression can prevent senescence of cardiac stem cells [60]. A study showed that the turnover or renewal rate of cardiomyocytes in young adults was approximately 1% annually, and this was significantly reduced to 0.45% in the hearts of the elderly [6]. Subsequently, direct delivery of cardiac stem cells/cardiac progenitor cells to the heart, and the development of agents that enhance the function of endogenous cardiac stem cells or progenitor cells represent promising therapeutic strategies in the process of senescent myocardium.

3.4. Dysregulation of microRNAs (miRNAs)

Several recent studies implicated the roles of miRNAs as novel cellular senescence regulators [61,62]. MiRNAs are a novel class of small non-coding RNA, which function as endogenous suppressors of gene expression through mRNA degradation and/or translational inhibition mainly by binding to 3′-untranslated region (3′-UTR) of target mRNAs [63,64]. As a center gene modulator, many essential biological

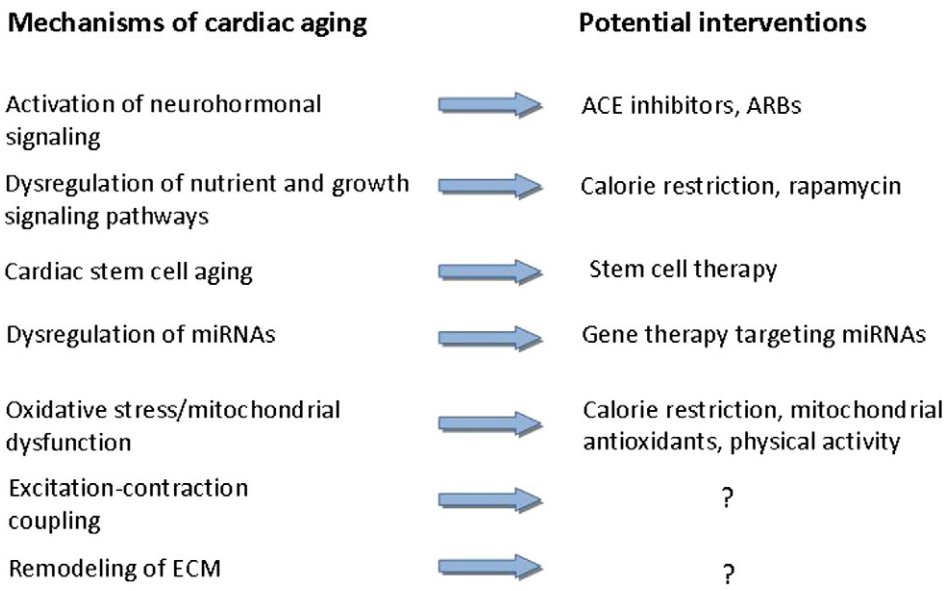

Fig. 2. Potential cardiac aging interventions which target specific pathophysiological mechanisms during cardiac aging process. ACE: angiotensin-converting enzyme, ARBs: angiotensin II receptor blockers, miRNAs: microRNAs.

processes are regulated by miRNAs, including proliferation, apoptosis, necrosis, autophagy, and stress responses [65]. It has been demonstrated that 65 miRNAs were differentially expressed in the old versus young mouse hearts, half of which belong to 11 miRNA clusters, implicating these clusters as a major contributor to the complex regulation of gene expression during heart aging [61]. MiRNA-22 was shown to be involved in aging-related cardiac fibrosis, whose overexpression contributed to cellular senescence and migration of cardiac fibroblasts [66]. A recent study has identified the aging-induced expression of miR-34a as a key mechanism that regulates cardiac contractile function during aging, by inducing DNA damage responses and telomere attrition [67]. In previous studies, the members of miR-17-92 cluster, including miR-18a, -19a, and -19b, were all downregulated in failure-prone heart of aged mice as well as in cardiac biopsies of idiopathic cardiomyopathy patients at old age and the inhibition of miR-18/19 in cardiomyocytes contributed to collagen synthesis [68,69]. Thus, pharmacological modulation of aging-related miRs might become a promising strategy to combat cardiovascular aging in a clinical setting.

3.5. Oxidative stress and mitochondrial dysfunction

There is evidence that oxidative stress and impaired antioxidant defense mechanisms are the major contributors to the cardiovascular aging process [70,71]. Oxidative stress develops as a consequence of excessive generation of reactive oxygen species (ROS), by enzymes such as NADPH (nicotinamide adenine dinucleotide phosphate) oxidase, uncoupled nitric oxide synthase, and xanthine oxidase, by the mitochondrial electron transport chain, and as a result of reduced antioxidant capacity [71,72]. Elevated oxidative stress in the senescent myocardium has several consequences such as enhanced protein oxidation/nitration, reduced bioavailability, lipofuscin formation, activation of inflammatory response, antioxidative stress response, apoptosis, and endoplasmic reticulum (ER) stress (Fig. 3) [71,73]. It is interesting to point out that the endothelial nitric oxide synthase (eNOS) dysfunction associated with ROS production, plays an important role in microvascular dysfunction and impaired ventricular contractility in elderly patients [74]. Increasing evidence suggests that abnormal mitochondrial ROS production and impaired ROS detoxification contribute

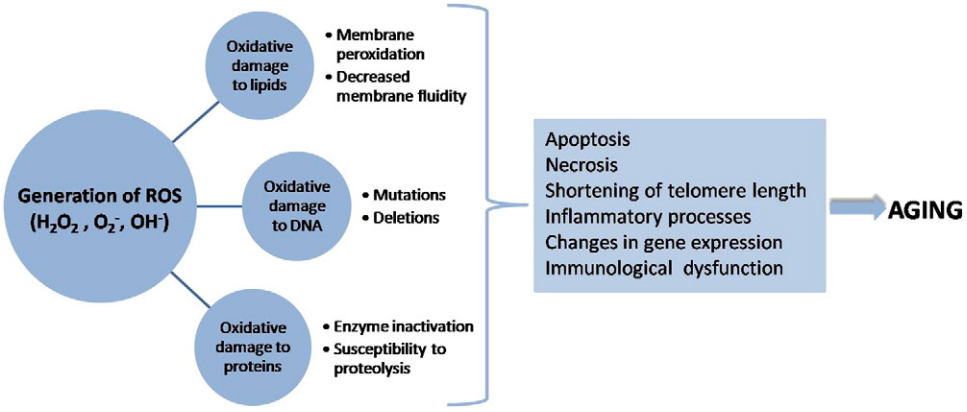

Fig. 3. The putative mechanisms of oxidative stress in the pathophysiology of senescence. The production of ROS causes oxidative damage to proteins, lipids and DNA, leading to the dysregulation of redox-sensitive signaling pathways (necrosis, apoptosis, cell death pathways, inflammatory processes, changes in gene expression, immunological dysfunction). ROS: reactive oxygen species.

to mitochondrial dysfunction and cardiomyopathy in old age [75,76]. This is in agreement with the mitochondrial free-radical theory of aging, which proposes that excessive mitochondrial ROS damages mitochondrial DNA and proteins, causing mitochondrial dysfunction and further increase in ROS production (the "vicious cycle" of ROS-induced ROS release), contributing to aging through both direct damage to cellular macromolecules and interference with normal signaling and energetics (Figs. 3, 4) [71]. The putative mechanisms of oxidative stress in the pathophysiology of senescence are summarized in Fig. 3.

4. Functional changes

4.1. Systolic function

Despite the various age-related changes in left ventricular (LV) structure, the LV ejection fraction (EF), the most commonly used clinical measure of LV systolic performance, is preserved during aging (normal average EF > 65%) [77]. However, very few healthy, sedentary, community-dwelling older individuals highly screened to exclude clinical and occult coronary disease have an EF < 50%, a value indicative of impaired LV systolic function [36]. The intrinsic contractility decreases during aging, partly due to the molecular changes considered earlier: decreased β-adrenergic responsiveness and impaired Ca^{+2} handling.

It is with exercise, that the effects of aging are most evident (Table 1). An overall decrease in exercise tolerance is evident in the progressive decline in VO_2max, starting at age 20–30 and falling by approximately 10% per decade [77]. Additionally, the rate of this decline progressively increases with age. The decrease of VO_2max in aging is due to a parallel reduction of both cardiac output and arteriovenous oxygen difference. During exercise the stroke volume increase is similar in young and older, but the mechanism of this increase is different. The elderly tends to augment stroke volume more through LV dilatation with an end-diastolic volume increase, while the young shows an increase in the ejection fraction without LV dilatation. Moreover, during exercise the older has a lower increase in heart rate and a greater raise in blood pressure [78]. In particular, in the aging human heart the maintaining of cardiac output during exercise is supported more heavily by the Franck–Starling mechanism and less by sympathetic stimulation demonstrating the presence of an age-related change in the adrenergic modulation [56]. Moreover, the maximum EF, which is achieved during exhaustive upright exercise, decreases with age in healthy persons [36]. The age-associated failure to augment EF with exercise is due to a remarkable age-associated deficit in the ability to reduce end-systolic volume index (ESVI) [36]. The acute end-systolic volume (ESV) reserve at age 85 is only about one-fifth of that at age 20, and there is a similar age-related loss of EF reserve [36]. Overall, the age-associated reduction in cardiac reserve during exercise is a result of multiple factors including increased vascular afterload, arterial-ventricular load mismatching, reduced intrinsic myocardial contractility, impaired autonomic regulation, and physical deconditioning. All the age-related changes in aerobic capacity and indexes of cardiac performance during exercise are shown in Table 1.

Table 1
Age-related changes in aerobic capacity and indexes of cardiac performance during exercise.

Parameter	Age-related changes
Oxygen consumption	Decrease
$(A\text{-}V)O_2$	Decrease
Cardiac index	Decrease
Stroke volume	Unchanged
Heart rate	Decrease
LV contractility	Decrease
Ejection fraction	Decrease
Responsiveness to β-adrenergic stimulation	Decrease

$(A\text{-}V)O_2$: arterial–venous oxygen concentration.
LV: left ventricular.

With aging, several changes occur in the right ventricle (RV) and the pulmonary vascular system. The pulmonary artery pressure and vascular resistance mildly increase with normal aging, most probably secondary to an increase in arterial stiffness of the pulmonary vasculature [10,79,80]. RVEF remains relatively well preserved with aging, as does LV ejection fraction. However, the global systolic strain is also reduced, with differential reductions in basal and mid segmental strain with age [81]. Myocyte loss and subsequent replacement by fibrosis with aging are the possible mechanisms for the reduced strain. Maffessanti et al. [82] recently reported increases in RVEF with age in a large group of healthy subjects using three dimensional echocardiography, and similar increases in RVEF were observed with cardiac magnetic resonance imaging (CMRI) [11]. Changes in RV systolic reserve with exercise have not been well studied but most likely parallel the small decline seen in LV systolic reserve [83].

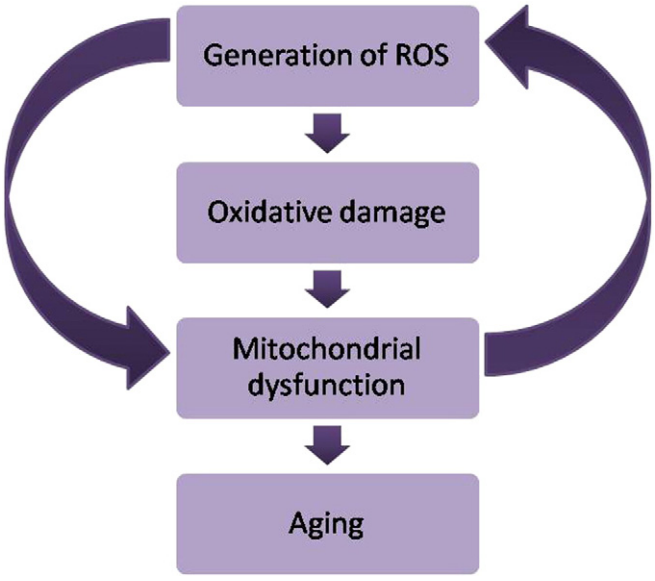

Fig. 4. The mitochondrial free-radical theory of aging, which proposes the "vicious cycle" of ROS-induced ROS release. The mitochondrial production of ROS damages mitochondrial DNA and proteins, causing mitochondrial dysfunction which in turn induces further increase in ROS production. ROS: reactive oxygen species.

4.2. Diastolic function

In contrast to systolic function, there are a number of changes in the diastolic phase of the cardiac cycle that occur with aging. The LV early diastolic filling rate progressively slows after the age of 20 years, so that by 80 years the rate is reduced, on average, up to 50% [36,84–86]. Accumulation of extracellular matrix material in the LV myocardium, fibrosis and slowing in Ca^{+2} activation from the preceding systole is the possible mechanisms for a reduced early diastolic LV filling rate. Despite the slowing of LV filling in early diastolic period, more filling occurs in late diastole, due in part to a more vigorous atrial contraction. Consequently, the E/A ratio of mitral flow is decreased from 2:1 in an adult to 1:1 at the age of 60 years, reflecting the importance of atrial contraction in LV filling [36] and interpreting the low tolerance during atrial fibrillation that is often observed in these patients.

Although the rate of early diastolic LV filling is reduced, LV end-diastolic volume does not decrease with age [86,87]. Additionally, the changes in end-diastolic volume during postural maneuvers that alter venous return are decreased in older subjects. During vigorous exercise, despite a reduction in the LV early diastolic filling rate, the LV at end diastole is greater in older than in younger men [86]. This also has been attributed to a decrease in LV compliance. Although end-diastolic volume (EDV) does not decrease with aging, the end-diastolic pressure is often higher in older subjects, particularly during exercise

[87].Consequently, the abovementioned structural changes in aged myocardium lead to development of diastolic heart failure, the most common form (40–80%) of heart failure in old people [87].

The changes in RV diastolic function are analogous to changes in LV diastolic filling profiles. Doppler indices, reflective of flow pattern, demonstrate a reduced early RV diastolic filling, increased late filling, and reduced myocardial diastolic velocities [10]. Indeed, A RV functional analysis by two-dimensional strain demonstrated that early diastolic strain rate decreases, with a corresponding increase in late diastolic strain rate during ventricular senescence [81]. Focal collagen deposition with increased fibrosis and impaired calcium uptake of the cardiomyocytes in aged myocardium leads to slow and incomplete RV relaxation [81].

4.3. Changes in conduction system

There is a negligible age-related decrease in the resting heart rate, but a marked decrease in the maximum heart rate in response to exercise or other stressors [36]. This inability to raise the heart rate to high levels during exercise is reflected in lower cardiac output reserve in older subjects and contributes to declining aerobic capacity in advancing age. Moreover, heart rate (HR) variability declines steadily with age. Reduced HR variability, an indicator of dysregulation of the autonomic nervous system commonly found in older individuals, has been associated with increased morbidity and mortality [88].

Degeneration of the conduction system and nodal pacemaker is thought to begin after the seventh decade of life and ion channel alterations, along with β-adrenergic receptor down regulation and signaling impairment, have been reported as physiological substrates for tachyarrhythmias or bradyarrhythmias in the elderly [89–92]. Thus, an increase in the prevalence and complexity of both supraventricular and ventricular arrhythmias, whether detected by resting electrocardiography (ECG), ambulatory monitoring, or exercise testing, occurs in otherwise healthy older patients in comparison to younger persons. Isolated atrial premature beats (APBs) appear on resting ECG in 5% to 10% of subjects older than 60 years and are generally not associated with heart disease. Over a 10-year mean follow-up period, isolated APBs, even if frequent, were not predictive of increased cardiac risk in elderly in the Baltimore Longitudinal Study on Aging (BLSA) [36]. Twenty-four-hour ambulatory monitoring studies have demonstrated short runs of PSVT (usually 3 to 5 beats) in 13–50% of clinically healthy older persons [93,94]. Although the presence of nonsustained PSVT did not predict an increase in risk of a future coronary event in BLSA subjects, 15% of those with PSVT later developed de novo AF, compared with fewer than 1% of subjects without PSVT [36]. Although those individuals with exercise-induced PSVT were not at a greater risk for coronary events over a multi-year follow-up, 10% developed a spontaneous atrial tachyarrhythmia compared with only 2% of the control group. Thus, PSVT at rest or induced by exercise is an indicator for increased risk for AF in some healthy individuals during aging. Another risk factor for AF may be the increase in left atrial size that accompanies advancing age in otherwise healthy persons [36,95]. Data available in older subjects supports that the median age of patients with AF is 75 years, with prevalence of 2.3% and 5.9% in people older than 40 years and 65 years, respectively. Approximately 70% of individuals with AF are between 65 and 85 years of age [96].

There is evidence for a marked age-associated increase in the prevalence and complexity of ventricular ectopy (VE), both at rest and during exercise, at least in men. Ventricular ectopy is a very common finding with ambulatory ECG monitoring in the elderly (>80%) [97]. However, in healthy BLSA volunteers with a normal ST-segment response to treadmill exercise, isolated VE occurred at rest in 8.6% of men over the age 60 years compared with only 0.5% in those 20- to 40-years-old. Neither the prevalence nor the complexity of resting VE was a determinant of future coronary events over a 10-year mean follow-up period in healthy BLSA volunteers [36,98]. Isolated VE during or after maximal treadmill exercise increased from 11% in the third to 57% in the ninth decade in apparently healthy BLSA volunteers [36,99]. It is noteworthy that the exercise-induced nonsustained ventricular tachycardia (NSVT) did not independently increase the risk of total mortality in asymptomatic BLSA volunteers [100].

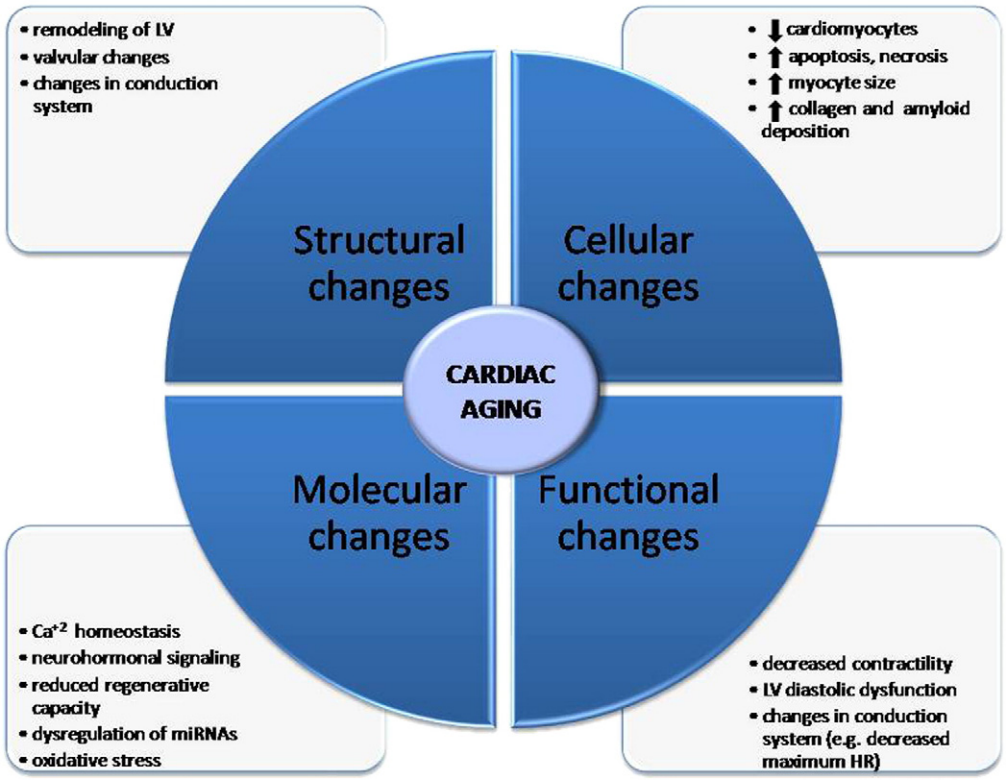

Fig. 5. The multifactorial changes affecting myocardium at structural, cellular, molecular and functional levels during normal aging. LV: left ventricular, miRNAs: microRNAs, HR: heart rate.

The multifactorial changes affecting myocardium at structural, cellular, molecular and functional levels during normal aging are shown in Fig. 5.

It should be noted that aging is not a homogenous process. The changes with age occur in everyone but not necessarily at the same rate, therefore accounting for the difference seen in some people between chronologic age and physiologic age. Thus, the "rate of aging myocardium" is influenced by multiple factors, including genetic make-up, lifestyle choices and environmental exposures. A Danish twin study found that genetics accounted for about 25% of the variation in longevity among twins, and environmental factors accounted for about 50% [101]. It has been widely documented that the physical conditioning of older individuals can substantially increase their maximum aerobic work capacity and peak oxygen consumption. The extent to which this conditioning effect results from enhanced central cardiac performance or from augmented peripheral circulatory and O_2 utilization mechanisms depends on the type and degree of conditioning achieved, the gender and the genetic basis [102]. A longitudinal study in older males shows that an enhanced physical conditioning status increases O_2 consumption and work capacity, partly due to increases in the maximum cardiac output by increasing the maximum systolic volume (SV), and partly due to increases in the atrioventricular O_2 utilization [103]. The increase in maximum SV is due to a greater reduction in ESV [103] and a concomitant increase in LV ejection fraction (LVEF), as the effect of conditioning status to increase LV end-diastolic volume during exercise is minimal [104]. In contrast to the improved LVEF, the maximum HR of older persons does not vary with physical conditioning status. Moreover, there is no strong evidence that physical conditioning of older subjects can offset the age-associated deficiency in sympathetic modulation of cardiac performance. In the molecular level, the physical activity increases the expression and the activity of antioxidant enzymes, with consequent reduction of ROS modifying the oxidative damage during cardiovascular aging [105].

The improved understanding on the pathophysiological mechanisms of cardiac aging has led to promising advancements in the development of cardiac aging interventions. Recent evidence supports the potential of different therapeutic strategies to delay or treat cardiac aging, ranging from calorie restriction to pharmacologic interventions (rapamycin, angiotensin receptor blockers, and the antioxidant peptide SS-31), recombinant protein therapy [IGF-1 and growth differentiation factor 11 (GDF-11)], gene therapy (miRNAs), and cardiac stem cell therapy (Fig. 2) [48]. However, further studies are required to evaluate the therapeutic potential of the novel perspectives in clinical practice.

In conclusion, cardiac aging is characterized by a series of complex events of ventricle and valvular changes involving left ventricular hypertrophy, diastolic dysfunction, valvular degeneration and fibrosis, and decreased maximal exercise capacity. These changes are identified at structural, cellular, molecular and functional levels making the aged myocardium more susceptible to stress, leading to a high prevalence of cardiovascular diseases (heart failure, atrial fibrillation, left ventricular hypertrophy, coronary artery disease) in the elderly population. The aging process is genetically programmed but modified by environmental influences, so that the rate of aging can vary widely among people. The elucidation of the mechanisms contributing to cardiac aging in healthy heart would help to identify early pathophysiological changes and guide the development of novel interventions that target specific mechanisms to delay cardiac aging in future.

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