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Review

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

ES Nakou *, FI Parthenakis, EM Kallergis, ME Marketou, KS Nakos, PE Vardas

Department of Cardiology, Heraklion University Hospital, 7100, Voutes, Heraklion-Crete, Greece

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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,

* Corresponding author.
E-mail address: EleniSNakou@yahoo.gr (E.S. Nakou).

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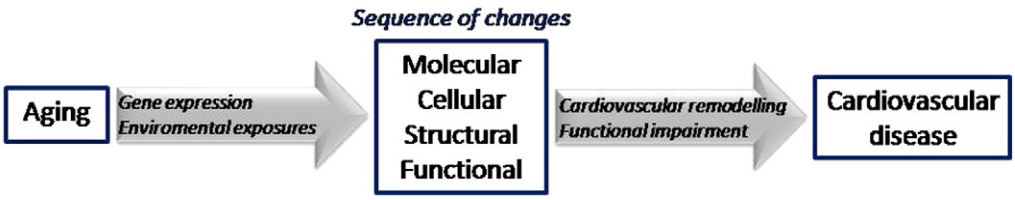

Fig. 1. The pathophysiological pathway leading in cardiovascular disease in aged myocardium.

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].