Ageing Research Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Quality control systems in cardiac aging

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ARTICLE INFO

Article history:
Received 8 November 2014
Received in revised form 2 February 2015
Accepted 12 February 2015
Available online xxx

Keywords:
Quality control
Aging
Heart
Cardiac function
Proteostasis

ABSTRACT

Cardiac aging is an intrinsic process that results in impaired cardiac function, along with cellular and molecular changes. These degenerative changes are intimately associated with quality control mechanisms. This review provides a general overview of the clinical and cellular changes which manifest in cardiac aging, and the quality control mechanisms involved in maintaining homeostasis and retarding aging. These mechanisms include autophagy, ubiquitin-mediated turnover, apoptosis, mitochondrial quality control and cardiac matrix homeostasis. Finally, we discuss aging interventions that have been observed to impact cardiac health outcomes. These include caloric restriction, rapamycin, resveratrol, GDF11, mitochondrial antioxidants and cardiolipin-targeted therapeutics. A greater understanding of the quality control mechanisms that promote cardiac homeostasis will help to understand the benefits of these interventions, and hopefully lead to further improved therapeutic modalities.

Contents

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http://dx.doi.org/10.1016/j.arr.2015.02.003
1568-1637/

1. Introduction

Cardiac aging is an intrinsic process that results in impaired cardiac function, along with cellular and molecular changes. These degenerative changes are intimately associated with quality control mechanisms. This review provides a general overview of the clinical and cellular changes which manifest in cardiac aging, and the quality control mechanisms involved in maintaining homeostasis and retarding aging. Finally, we discuss aging interventions that have been observed to impact cardiac health outcomes.

2. Overview of cardiac aging

2.1. Human cardiac aging

A growing body of studies examining human aging and centenarians are beginning to address what healthy aging means for the CV system (Galioto et al., 2008). Centenarians have lower prevalence of CV diseases, hypertension, myocardial infarction, angina, and diabetes than younger persons (ages 70–99 years) (Selim et al., 2005; Galioto et al., 2008). This trend toward protection from CV-related causes of death (hypertension, heart disease, diabetes) is also present in their descendants, pointing to a genetic or epigenetic healthy aging profile (Perls and Terry, 2003). Multiple studies have followed CV risks factors and CV health in long-lived populations and while some aspects of disease incidence and primary risk factors differ between groups, the recurring conclusion is that a boost to cardiac health occurring early in life (either through genetics or lifestyle) and maintained through life (also by some combination of genetics and lifestyle) is a common piece of the longevity puzzle (Curb et al., 1990; Yashin et al., 2006). As more studies (and the cohorts within them) mature, there will be more data available on why some humans succumb to aging-related disease early, while others last into their 10th decade.

The Framingham Heart Study and the Baltimore Longitudinal Study on Aging demonstrated that in apparently healthy adults, aging is associated with increase in left ventricular wall thickness measured by echocardiography. The Doppler measurement of the E/A ratio, the ratio between early (E) and late (A) diastolic LV filling, declines dramatically with age (Dai and Rabinovitch, 2009; Dai et al., 2009). This decline in the E/A ratio suggests that a greater portion of blood filling in the LV results from late diastolic filling as opposed to early diastolic filling, which is clinically defined as diastolic dysfunction or heart failure with preserved ejection fraction (HFpEF). The prevalence of LV hypertrophy and diastolic dysfunction significantly increased in the elderly (Bursi et al., 2006), even in an apparently healthy elderly population without hypertension, suggesting that intrinsic cardiac aging may manifest as the above changes.

Although systolic function determined from ejection fraction is relatively preserved at rest in the elderly, exercise capacity and cardiovascular reserve after prolonged exercise significantly declines with age (Correia et al., 2002). Aging also contributes to the decline of the maximal heart rate during strenuous exercise, but does not affect the resting heart rate when lying face up (Fleg et al., 1995). The decrease in exercise capacity in the elderly is attributed to a modest decrease in ejection fraction after maximal exercise and a prominent decline in maximal heart rate at peak exercise. Likewise, there is age-dependent decline in maximal cardiac index, another measure of systolic function calculated as the cardiac output normalized to the body surface area, which is mostly due to a decline in maximal heart rate after strenuous exercise.

The increased fraction of LV filling performed by atrial contraction in diastolic dysfunction also increases atrial pressure, adversely contributing to atrial hypertrophy and dilatation and subsequently increasing the risk of atrial fibrillation, consistent with the significant age-dependent increase in the prevalence of atrial fibrillation (Lakatta, 2003; Lakatta and Levy, 2003a,b). Atrial fibrillation adversely affects exercise capacity in the geriatric population. It also predisposes to the development of HFpEF. Indeed, HFpEF accounts for more than half of all heart failure cases in patients older than 75 years old, especially in those without structural or ischemic heart diseases.

Valvular changes in old age include myxomatous degeneration, deposition of collagen and calcium leading to sclerosis of the valves. Aortic valve sclerosis is present in 30–80% of the elderly (Stewart et al., 1997; Nassimiha et al., 2001; Karavidas et al., 2010), which is detected by echocardiography as calcification of aortic valve leaflets and aortic annulus (Otto et al., 1999; Freeman and Otto, 2005). Age-related aortic valve sclerosis predisposes to the development of aortic stenosis and increased leaflet calcification and decreased leaflet mobility may predict the progression to aortic stenosis. Hypertension, LV hypertrophy, hyperlipidemia, smoking, end-stage renal disease and congenital bicuspid aortic valves are important risk factors for the progression to aortic valve stenosis (Olsen et al., 2005).

In the elderly, fibrosis and valvular calcification are the most common factors contributing to the development of aortic stenosis, which occurs when the aortic valve opening narrows due to the stiffening and calcification of the aortic valve leaflets (Olsen et al., 2005). This narrowing prevents effective blood pumping through aortic valve, generating a pressure gradient between the aorta and the left ventricle. To compensate for this obstruction, the walls of the left ventricle thicken with myocardial hypertrophy to maintain sufficient systolic function. Later in the progression, increased wall stress due to pressure overload causes the left ventricle to dilate, leading to deterioration of systolic function. In addition, aortic regurgitation, also related to the calcification of the aortic cusps and annulus, increases with age, and is present in 13–16% of the elderly population (Nassimiha et al., 2001). The presence of aortic regurgitation results in ineffective work of the left ventricle and volume overload that may lead to LV dilatation and systolic heart failure.

The above ventricular and valvular changes in cardiac aging compromise the cardiac functional reserve capacity as well as lower the threshold for development of heart failure (Correia et al., 2002). This makes the aged heart more susceptible to stress and disease-related challenges, leading to increased prevalence of heart failure and CV mortality in the geriatric population.

2.2. Large mammal models of cardiac aging

Canine hearts develop several aging changes, including myocardial hypertrophy, accumulation of lipofuscin and amyloid which

Please cite this article in press as: Quarles, E.K., et al., Quality control systems in cardiac aging. Ageing Res. Rev. (2015), http://dx.doi.org/10.1016/j.arr.2015.02.003