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REVIEW

Cardiac aging and heart disease in humans

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Abstract The world population continues to grow older rapidly, mostly because of declining fertility and increasing longevity. Since age represents the largest risk factor for cardiovascular disease, the prevalence of these pathologies increases dramatically with increasing age. In order to improve patient care and prevention for age-related cardiac diseases, insight should be gained from the analysis of processes involved in and leading to cardiac aging. It is from this perspective that we provide here an overview of changes associated with age in the heart on four levels: functional, structural, cellular and molecular. We highlight those changes that are in common with the development of the two major age-associated cardiac pathologies: heart failure and atrial fibrillation. These commonly affected processes in aging and cardiac pathophysiology may provide an explanation for the age risk factor in cardiac disease.

Keywords Heart · Aging · Heart failure · Atrial fibrillation

Introduction

The average lifespan of the human population is increasing worldwide, mostly because of declining fertility and increasing longevity. It has been predicted that, in 2035, nearly one in four individuals will be 65 years or older (Lakatta and Sollott 2002). With age being the dominant risk factor for the development of cardiovascular diseases, their prevalence increases dramatically with increasing age (Lakatta and Levy 2003). At the end of the twentieth century, Braunwald announced the emergence of two new epidemics of cardiovascular disease: heart failure and atrial fibrillation (Braunwald 1997). The prevalence of heart failure in the adult population in developed countries is 1–2%, which rises to >10% among persons 70 years or older (McMurray et al. 2012). This population can be divided into patients with a preserved ejection fraction (HFpEF)—representing around half of the patients (Lam et al. 2011)—and patients with a reduced ejection fraction (HFrEF). The same trend is seen for atrial fibrillation, with a prevalence rising from 0.12 - 0.16% in persons younger than 49 years, to 3.7–4.2% in persons aged 60–70 years, to 10–17% in persons aged 80 years or older (Zoni-Berisso et al. 2014). Since there is a clear association between aging of the population and increasing prevalence of cardiovascular disease, cardiovascular aging most likely affects pathophysiological pathways also implicated in the development of cardiovascular disease. Therefore, a better insight into cardiac aging may unravel factors implicated in cardiac pathophysiology and help towards improved prevention of human cardiovascular disease. In this review, we discuss four different levels of human cardiac aging: functional, structural, cellular and molecular. Since data on molecular changes associated with human cardiac aging are lacking, we rely on results obtained from studies on animal models for this part. For all findings, a link is made with data on human heart failure and atrial fibrillation, to highlight potential common pathways of cardiac aging and heart disease in humans.

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Functional changes of the aging heart

Diastolic function

The hallmark of cardiac aging is a decrease in left ventricular (LV) diastolic function. Normal diastolic filling can be divided into two phases: passive filling early during diastole ('E') and active filling late during diastole by atrial contraction ('A'). With age, the rate of filling declines. The bulk of ventricular filling shifts to later in diastole and there is significant atrial enlargement. Therefore, the atrium assumes a greater portion of the total end diastolic volume and the E/A ratio decreases (Strait and Lakatta 2012). Age-related diastolic dysfunction is linked to the epidemic of HFpEF (Desai and Fang 2008), a disease that was previously named diastolic heart failure. HFpEF patients usually display diastolic abnormalities including delayed early relaxation, myocardial and myocyte stiffening, and associated changes in filling dynamics (Sharma and Kass 2014). Diastolic dysfunction is also a major problem for patients with atrial fibrillation. These patients—even those with paroxystic or non-permanent atrial fibrillation—have reduced atrial contraction due to atrial remodeling and are therefore not able to increase the late LV filling during diastole to preserve their ejection fraction. Therefore, these patients are at increased risk for the development of heart failure (Keller and Howlett 2016).

Systolic function

Although the LV ejection fraction—which is the most commonly used measure of LV systolic performance—is preserved during aging, systolic function is affected (Lakatta and Levy 2003). This is reflected by an age-associated reduction in cardiac reserve during exercise. Factors involved in this reduction include a decrease of myocardial contractility, and a decrease in maximum heart rate and maximum ejection fraction achieved during exercise. Decreased cardiac functional reserve is associated with heart failure in general.

Electrical function

In the cardiac conduction system, aging is associated with a vital reduction of pacemaker cells in the sinoatrial node. This is reflected by an increased incidence of sinus dysfunction in the elderly and manifests itself by palpitations, dizziness, syncope with persistent fatigue and confusion (Jones 2006). In addition, tissue remodeling affects the functioning of the atrioventricular node, the bundle of His and the bundle branches. The resulting changes in depolarization and repolarization of the atria and the ventricles are reflected by age-associated changes in ECG measurements: An increase in P-wave duration, P–R interval and Q–T interval, a decrease in QRS voltage and T-wave voltage and a leftward shift of the QRS axis (Strait and Lakatta 2012). In addition, the prevalence of both atrial and ventricular ectopic beats increases. The alterations of the cardiac electrical system are reflected by an increased predisposition to cardiac arrhythmias. Bradycardia and chronotropic incompetency caused by sinus node dysfunction or other conduction system abnormalities are responsible for the skewed age distribution among pacemaker recipients: 70–80% of all pacemakers are implanted in patients 65 years of age or older (Gregoratos 1999). Among the tachyarrhythmias, atrial fibrillation is the most common arrhythmia in the elderly. As mentioned above, with the appearance of diastolic dysfunction, the atria make a larger contribution to ventricular filling in older adults than in younger adults. Therefore, elderly patients with atrial fibrillation and hence diminished atrial contraction have markedly reduced diastolic volumes. These factors combined increase the risk for the development of heart failure (Keller and Howlett 2016).

Structural changes of the aging heart

Ventricular structure

On a structural level, the most striking phenomenon seen with age is an increase in the thickness of the LV wall as a result of increased cardiomyocyte size. This LV hypertrophy has been identified by longitudinal clinical trials such as The Framingham Heart Study and the Baltimore Longitudinal Study on Aging (Lakatta and Levy 2003). LV hypertrophy is mostly seen as a compensatory response after the loss of cardiomyocytes with aging (Olivetti et al. 1991). There have been conflicting data concerning the evolution of LV mass with age, but recent analyses tend towards no effect on mass (Akasheva et al. 2015) or a sex-specific decrease in men only (Strait and Lakatta 2012). LV dimension decreases with age, reflected by an increase in the mass/volume ratio and a decrease in LV end-diastolic volume (Cheng et al. 2009). Therefore, aging is associated with LV concentric hypertrophy. This hypertrophy affects the LV in an asymmetrical way, mostly affecting the interventricular septum and leading to a redistribution of cardiac muscle, explaining the lack of effect on total cardiac mass. As reviewed by Katz and Rolett (2016), concentric hypertrophy and a decreased LV cavity volume are hallmarks of HFpEF. In this disease, further evolution of concentric hypertrophy may eventually contribute to the development of fibrosis, arrhythmias, progressive myocardial deterioration, and end-stage heart failure (Rockey et al. 2015).

Atrial structure

As mentioned above, in the elderly, atrial contraction plays a much greater role in LV filling during diastole than in the young population. This change in function is associated with the

development of atrial hypertrophy and dilation. Left atrial size has been associated with the presence of atrial fibrillation, indicating that atrial remodeling favors the development of this arrhythmia (Lam et al. 2017). Two important players of age-related structural remodeling of the heart—LV concentric hypertrophy and atrial dilation—are therefore associated with the two main cardiac pathologies of old age: HFpEF and atrial fibrillation. These two pathologies often occur together, with two-thirds of HFpEF patients at some point presenting with atrial fibrillation and with most patients first developing atrial fibrillation and then heart failure (Santhanakrishnan et al. 2016).

Cellular changes of the aging heart

Fibrosis

Remodeling at the cellular level includes a loss of cardiomyocytes and sinoatrial node pacemaker cells with age (Keller and Howlett 2016), and may contribute to the compensatory development of hypertrophy. This compensatory remodeling process may also involve changes in the composition of the extracellular matrix. The function of the extracellular matrix is to maintain the myocardial structure throughout the cardiac cycle. Hereby it plays an important role in the elastic and viscous properties of the LV. Changes in both the quantity of fibrosis and in the type of collagen fibers have been associated with old age in human hearts. Increased age-related fibrosis has been found in the cardiac conduction system (the sinoatrial node, the atrio-ventricular node, the His bundle and the left bundle branch) (Song et al. 1999), as well as in LV tissue (Gazoti Debessa et al. 2001). The latter study also identified qualitative differences in collagen deposition between old and young hearts, with a shift towards collagen type I fibers with age. It is easy to imagine that changes in the elastic properties of the LV caused by fibrosis may eventually lead to diastolic dysfunction. Indeed, in hypertensive heart disease patients with HFpEF, more severe diastolic dysfunction has been associated with a more active fibrotic process (Martos et al. 2007). The same authors also showed that serological levels of cardiac fibrotic markers may be more powerful for the diagnosis of HFpEF than the commonly used heart failure marker BNP (B-type natriuretic peptide) (Martos et al. 2009). The development and progression of atrial fibrosis are strongly associated with atrial fibrillation (Burstein and Nattel 2008). Proliferation of cardiac fibroblasts and deposition of collagen in the atria with age will affect the electrophysiological properties of the myocardium and might lower the threshold for the development of atrial arrhythmias. Besides atrial fibrosis, ventricular fibrotic changes have also been identified in atrial fibrillation patients (Ling et al. 2012), and the extent of these changes has been found to be associated with the type of atrial fibrillation. In patients with permanent or persistent arrhythmia, more pronounced changes were found than in patients with paroxysmal arrhythmia (Dzeshka et al. 2015).

Amyloid deposition

Another histopathological change found in cardiac tissue of old people is amyloid deposition. An autopsy study on a Finnish population aged 85 or over showed the presence of amyloid deposits in 25%, with a strong correlation between the presence of amyloid and the age at time of death (Tanskanen et al. 2008). Amyloid found in heart of the elderly is derived from the transthyretin molecule. With age, this molecule may become structurally unstable and result in the development of misfolded intermediates that aggregate and precipitate as amyloid, mainly in the heart (Chung et al. 2001). In some cases, amyloid deposition in the heart occurs at a level that will lead to the progressive development of heart failure. This infiltrative cardiomyopathy is defined as systemic senile amyloidosis (SSA) (Ng et al. 2005). About one-third of the patients present with conduction and/or electrophysiological abnormalities: atrial fibrillation, atrioventricular block and left bundle-branch block (Rapezzi et al. 2009). Amyloid deposits are found in both the atrium and the ventricle, albeit that the precursor protein from which the amyloid is derived differs according to the cardiac compartment (Falk 2012). Atrium-restricted amyloidosis, or isolated atrial amyloidosis (IAA), is far more common than SSA, with a prevalence >90% in the ninth decade of life (Steiner 1987). IAA is caused by the deposit of amyloid fibers derived from ANP (atrial natriuretic peptide), a peptide hormone synthesized and secreted predominantly by atrial cardiomyocytes. Atrial samples from patients with atrial fibrillation have been shown to contain significantly higher amounts of ANP-derived amyloid than samples from patients in sinus rhythm (Rocken et al. 2002). Since amyloid affects myocyte contractility and conduction, it has therefore been hypothesized that it enhances the susceptibility for atrial fibrillation.

Molecular changes of the aging heart

There are numerous data on molecular pathways implicated in cardiac aging. These studies mostly concern analyses of animal models, whereas data on molecular changes associated with human cardiac aging are lacking. Therefore, for this part of the review, we will discuss animal-based data. Among the many molecular pathways associated with cardiac aging, we will focus on mitochondrial function, calcium signaling and neurohormonal signaling.

Mitochondrial function

Cardiac function requires an enormous amount of energy and mitochondria are critical for the required ATP production in the

myocardium. They also play a fundamental role in the survival and function of cardiomyocytes (Ren et al. 2010). The implication of mitochondrial dysfunction in cardiac aging has been nicely reviewed by Tocchi et al. (2015). They describe that cardiac senescence is accompanied by a general decline in mitochondrial function, clonal expansion of dysfunctional mitochondria, increased production of reactive oxygen species (ROS), suppressed mitophagy and dysregulation of mitochondrial quality processes such as fusion and fission. Of these processes, the development of oxidative stress as a consequence of excessive ROS generation is the most frequently described phenomenon. The main sites of ROS generation are located within the electron transport chain in mitochondria. Since mitochondrial DNA lacks protective histones and is in close proximity to high levels of ROS, it is particularly susceptible to oxidation (Yakes and Van 1997). Besides damage to DNA, ROS also causes damage to proteins and lipids in the mitochondrion, leading to dysregulation of several pathways: necrosis, apoptosis, inflammation, changes in gene expression and immunological dysfunction (Nakou et al. 2016). The mitochondria free radical theory of aging states that the ROS-dependent dysregulation of these pathways impairs mitochondrial respiratory efficiency, leading to further ROS production in a vicious cycle (Tocchi et al. 2015). However, recently, a debate has started about the role of ROS in the aging process, since these molecules have been shown to also act as prolongevity signaling actors in some models (Martin-Fernandez and Gredilla 2016). In the context of cardiac disease, ample evidence exists for the existence of a pathogenic link between enhanced ROS production, mitochondrial dysfunction and the development of heart failure (Martin-Fernandez and Gredilla 2016). In addition, serum markers of oxidative stress have been found to be increased in patients with persistent atrial fibrillation (Neuman et al. 2007).

Calcium signaling

A study on mice provided a link between mitochondrial oxidative stress and atrial fibrillation through alterations of the type 2 ryanodine receptor (RyR2) (Xie et al. 2015). RyR2 is a calcium channel that mediates the release of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm, thereby triggering cardiac muscle contraction. Aging-associated mitochondrial dysfunction is also directly connected with other changes in calcium signaling: One of the proteins affected by oxidative damage with age is the sarcoplasmic reticulum Ca^{2+} ATPase pump (SERCA) (Babusikova et al. 2012). This enzyme catalyzes the hydrolysis of ATP coupled with the translocation of Ca^{2+} from the cytosol into the sarcoplasmic reticulum lumen, which causes relaxation of the cardiac muscle following the excitatory effect of high cytosolic calcium. Decreased activity of SERCA with age will therefore lead to prolongation of relaxation and thus diastolic dysfunction. SERCA has also been shown to be affected at the protein level, with expression decreasing with age (Feridooni et al. 2015), leading to the same effect on the Ca^{2+} transient. The activity of SERCA is inhibited by phospholamban (PLN) when the latter is unphosphorylated, and it has been shown that the SERCA/PLN ratio decreases with age, also leading to slower relaxation. Calcium enters the cell through L-type Ca^{2+} channels upon membrane depolarization, triggering the release of Ca^{2+} from the sarcoplasmic reticulum through RyR2 and cardiac muscle contraction. Although the density of the L-type Ca^{2+} channels does not seem to be affected by age, its function seems to decline: a reduction in Ca^{2+} transient amplitude as well as a slower inactivation of the channel has been associated with aging (Feridooni et al. 2015). The activity of the above-mentioned calcium-handling proteins (RyR2, SERCA, PLN) is regulated through phosphorylation by

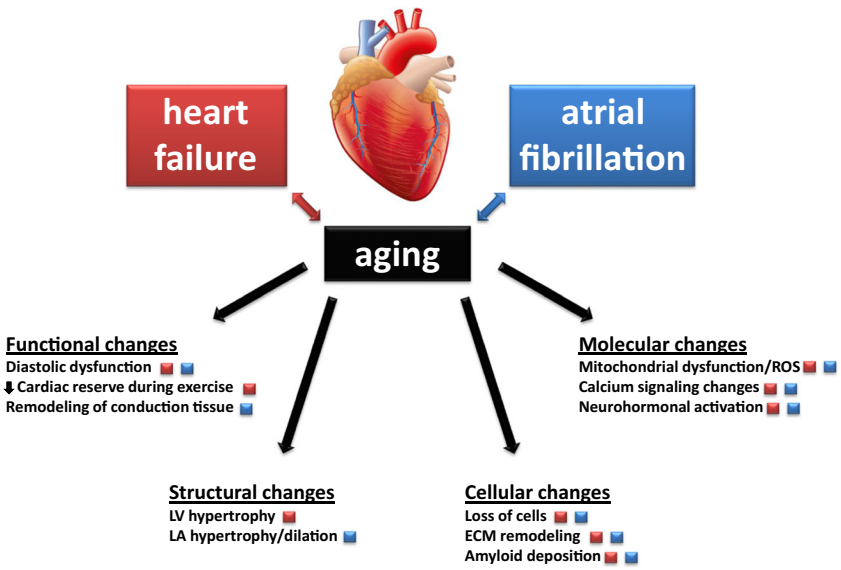

Fig. 1 Schematic overview of changes associated with cardiac aging and their link with heart failure and atrial fibrillation. *Red boxes* indicate changes associated with human heart failure, *blue boxes* indicate changes associated with human atrial fibrillation

calcium-/calmodulin-dependent protein kinase II (CaMKII). In concordance with an alteration of calcium signaling, aging has been found to be associated with both a decrease of CaMKII protein and of CaMKII-mediated phosphorylation of calcium-handling proteins (Xu and Narayanan 1998). In human heart failure, the activity of these calcium-handling proteins is similarly affected (Braunwald 2015). Both the protein level of SERCA and the SERCA/PLN ratio were found to be significantly reduced in failing human myocardium, indicating that reduced Ca^{2+} uptake in the sarcoplasmic reticulum is involved in the pathophysiology of heart failure (Meyer et al. 1995). Another study revealed increased phosphorylation of RyR2 by CaMKII in failing human myocardium, which might play a role in the development of pathological Ca^{2+} leak from the sarcoplasmic reticulum associated with a loss of contractility (Respress et al. 2012). Atrial fibrillation is even more strongly associated with calcium signaling abnormalities: The density of the L-type Ca^{2+} channels is reduced in myocytes from atria of chronic atrial fibrillation patients (Van Wagoner et al. 1999). As in heart failure, a sarcoplasmic reticulum Ca^{2+} leak is found, caused by hyperphosphorylation of RyR2 by CaMKII (Voigt et al. 2012). The importance of RyR2 in the pathophysiology of atrial fibrillation is underscored by the identification of mutations in this gene in atrial fibrillation patients (Bhuiyan et al. 2007; Di et al. 2014).

Neurohormonal signaling

The third molecular pathway involved in cardiac aging is neurohormonal signaling, which becomes chronically activated with age (Chiao and Rabinovitch 2015). The basic players of this pathway are the renin angiotensin aldosterone system (RAAS) and β-adrenergic signaling. Release of renin, primarily by the kidneys, stimulates the formation of angiotensin I and II, the latter of which is the most potent stimulator of aldosterone release by the adrenal glands (Verbrugge et al. 2015). RAAS plays an important role in regulating blood volume and systemic resistance. Several studies have revealed similarities between angiotensin II-treated heart and the aging heart, suggesting that angiotensin II may play a role in cardiac aging (Keller and Howlett 2016). These similarities consisted of the development of cardiac hypertrophy, fibrosis and diastolic dysfunction. In addition, ROS increases after chronic exposure to angiotensin II (Dai et al. 2012). In human heart failure, the activity of RAAS is increased and its maladaptive mechanisms may lead to adverse effects such as cardiac remodeling and sympathetic activation (Unger and Li 2004). Monitoring the serum levels of the different components of RAAS in heart failure patients has been suggested as a guide to tailor individual therapy (Emdin et al. 2015). RAAS activation also seems to be arrhythmogenic, and this goes especially for atrial fibrillation (Iravanian and Dudley 2008). In this case, RAAS activation may lead to alterations in ion channels through increasing oxidative stress. Neurohormonal signaling also involves β-adrenergic receptors. These receptors regulate heart rate, myocardial contractility and ventricular structural remodeling after stimulation by catecholamines (noradrenaline and adrenaline). As pointed out above, response to exercise—which involves β-adrenergic stimulation—is altered in the elderly, affecting heart rate, cardiac contractility, cardiac output and ejection fraction. With aging, circulating catecholamine levels increase, leading to a reduction of β-adrenergic receptor density at the plasma membrane. This explains the reduced β-adrenergic responsivity observed with age, defined as β-adrenergic desensitization (Ferrara et al. 2014). In addition, chronic β-adrenergic stimulation may induce ROS production leading to heart damage (Dai et al. 2012). In human heart failure, a similar situation occurs. At the early stages of the disease, sympathetic activity is increased by high levels of catecholamines, in order to preserve cardiac output. However, as is seen with aging, chronic β-adrenergic stimulation will lead to β-adrenergic desensitization, which will give rise to further pathologic changes and remodeling of the heart in these patients (Najafi et al. 2016). The implication of β-adrenergic signaling in atrial fibrillation is less clear. However, in post-operative atrial fibrillation—one of the most frequent complications of cardiac surgery—sympathetic activation has been shown to contribute to the onset of the arrhythmia, by altering atrial refractoriness and promoting ectopic activity (Maesen et al. 2012).

Conclusion

As summarized in Fig. 1, we here provide a non-exhaustive overview of changes associated with cardiac aging in humans and highlight overlaps with the age-related cardiac diseases of heart failure and atrial fibrillation. This highlights processes common to both aging and cardiac pathophysiology, which may provide an explanation of the age risk factor for these diseases on different levels. Thus far, our knowledge of molecular changes in cardiac aging is based mainly on animal models. Therefore, to improve the overall picture of the common pathways in human cardiac aging and disease, experiments should be performed to decipher molecular pathways involved in cardiac aging in man.

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Compliance with ethical standards

Conflict of interests Marja Steenman declares that she has no conflict of interest.

Gilles Lande declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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