Sex Differences in the Biology and Pathology of the Aging Heart

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ABSTRACT

The knowledge that advanced age is a major risk factor for cardiovascular disease (CVD) has stimulated interest in cardiac aging. Understanding how the heart remodels with age can help us appreciate why older individuals are more likely to acquire heart disease. Growing evidence in both humans and animals shows that the heart exhibits distinct structural and functional changes as a consequence of age. These changes occur even in the absence of overt cardiovascular disease and are often maladaptive. For example, atrial hypertrophy and fibrosis may increase susceptibility to atrial fibrillation in older adults. Age-dependent increases in left ventricular fibrosis, stiffness, and wall thickness promote diastolic dysfunction, predisposing to heart failure with preserved ejection fraction. The influence of age on the heart is evident at rest but is even more prominent during exercise. There is also evidence for sex-specific variation in age-associated remodelling. For instance, there is some evidence that the number of ventricular myocytes declines with age through apoptosis in men but not in women. This helps explain why older men are more likely to have heart failure with preserved ejection fraction. The in

RESUMÉ

Sachant qu’un âge avancé constitue en soi un important facteur de risque de maladie cardiovasculaire (MCV), on s’intéresse actuellement de plus en plus au phénomène du vieillissement cardiaque. Une meilleure compréhension des mécanismes du remodelage cardiaque au fil du temps pourrait aider à expliquer pourquoi les personnes âgées sont plus susceptibles de souffrir de maladie du cœur. Des données probantes croissantes, obtenues tant chez des modèles animaux qu’humains, montrent que le cœur subit des modifications structurelles et fonctionnelles précises au fil des années. Ces modifications surviennent même en l’absence de MCV avérée et sont souvent la conséquence d’une problématique adaptative. Par exemple, l’hypertrophie et la fibrose auriculaire peuvent accroître le risque de fibration auriculaire chez les adultes plus âgés. De même, l’augmentation liée à l’âge de la fibrose, de la rigidité et de l’épaisseur de la paroi ventriculaire gauche peut favoriser l’apparition d’une dysfonction diastolique qui évoluera vers une insuffisance cardiaque sans altération de la fraction d’éjection ventriculaire gauche. Les effets de l’âge

The incidence of cardiovascular disease (CVD) rises dramatically with age in men and women. The idea that age itself is a risk factor for the development of CVD has motivated interest in the field of cardiac aging. Growing clinical and experimental evidence demonstrates that the aging process promotes structural and functional remodelling of the heart, even in the absence of overt CVD. Whether these age-related modifications represent a disease phenotype is debated. However, these changes do render the aging heart more susceptible to CVD, as discussed in detail in this review.

This article reviews important structural modifications in the aging heart at both the macroscopic and microscopic levels. We also discuss the impact of age on heart function, with emphasis on the pacemaker, the conduction system, the atria, and the ventricles. Key molecular mechanisms involved, including altered calcium homeostasis, dysregulation of the ß-adrenergic and renin-angiotensin pathways, and mitochondrial dysfunction are also considered. Throughout the review, we highlight male/female differences in cardiac aging. The terms “age” and “aging” are used to refer to the effect of chronological age on the heart, although we discuss emerging evidence that biological age, measured as frailty, may exacerbate changes associated with cardiac aging.

Age-Associated Changes in Cardiac Structure

Macroscopic changes associated with cardiac aging

Normal cardiac aging is characterized by structural changes at both macroscopic and microscopic levels. Studies in humans have shown that epicardial adipose tissue deposition increases markedly with age. Calcification of specific
than women to experience heart failure with reduced ejection fraction. Emerging evidence from preclinical studies suggests that frailty rather than chronological age promotes adverse cardiac remodelling. Mechanisms implicated in cardiac aging include impaired calcium handling, excessive activation of the β-adrenergic and renin-angiotensin systems, and mitochondrial dysfunction. Further research into cardiac aging in both sexes is needed, because it may be possible to modify disease treatment if the substrate upon which the disease first develops is better understood.

regions, including the aortic valve leaflets, also occurs in older adults. In addition, there are changes in the gross morphologic structure of the heart. Atrial remodelling characterized by larger atrial size and volume occurs, although not until the eighth decade unless underlying disease treatment if the substrate upon which the disease fi
does not occur. Left ventricular (LV) wall thickness increases in healthy older adults, whereas LV systolic and diastolic volumes decline with age in both sexes. Whether LV mass is affected by age is controversial, although LV mass-to-volume ratios increase with age in both men and women. The major macroscopic changes in heart structure with age are illustrated in Figure 1.

Cellular cardiac aging

Age-dependent cardiac remodelling also occurs at the microscopic level. In humans, the number of sinoatrial node (SAN) pacemaker cells declines markedly with age. There is also some evidence that ventricular myocyte numbers may decline with age and that this may be more prominent in men than in women. The loss of myocytes may result from apoptosis, necrosis, or autophagy (or a combination), although limited regenerative ability of stem cells also may contribute. Age-related cell loss can, in theory, increase the mechanical burden on surviving myocytes and lead to compensatory hypertrophy. Morphometric analysis suggests that ventricular myocyte volume increases with age and that this may be more pronounced in men than in women. Still, the question of whether age-dependent myocyte loss and hypertrophy occur at different rates and through different mechanisms in male and female hearts has not been firmly established, and additional studies would be helpful in resolving this issue. Although the number of cardiomyocytes may decline with age, there is marked proliferation of cardiac fibroblasts, the cells that produce extracellular matrix and collagen. ' The accumulation of collagen leads to interstitial fibrosis in the atria, SANs, and ventricles of older adults. Key microscopic changes characteristic of cardiac aging are shown in Figure 1. Both gross and cellular changes in heart structure with age are believed to adversely affect myocardial function, as discussed in detail in the section Impact of Age on Cardiac Function.

Animal models exhibit the major age-associated structural changes seen in humans

Animal models have been used to explore many aspects of cardiac aging. Rats and mice have a 50% mortality rate at 24 months of age, comparable to that in 85-year-old humans, so most studies use 24-month-old rodents to model human aging. Many of the macroscopic changes characteristic of aging human hearts also occur in older animals. For example, epicardial fat deposition and aortic valve calcification are seen in older animals. There is also evidence for atrial hypertrophy and dilatation in older rodents, and LV wall thickness increases with age in older rats and mice. Microscopic changes observed in aging human hearts are also seen in older animals. Whether the number of pacemaker cells decreases with age in animals is unclear, but the expression of ion channels involved in SAN function declines with age in rats. Ventricular myocyte loss through apoptosis, along with an increase in the cross-sectional area of surviving cells, occurs in aging male nonhuman primates, although this is not seen in older female nonhuman primates. There also is a growing consensus that ventricular myocyte hypertrophy (increased length, width, and cross-sectional area) occurs in aging male rodents as well as in guinea pigs and rabbits. Whether ventricular myocyte hypertrophy occurs in myocytes from female aging rodents is less clear because some studies have reported increased cell length, width, and area, whereas others have not. This suggests that both concentric hypertrophy, associated with lateral growth of individual myocytes, and eccentric hypertrophy, linked to longitudinal cell growth, may occur in the aging male heart. As with humans, additional studies that investigate whether age-dependent myocyte loss and hypertrophy occur at the same rates and through the same mechanisms in both sexes would be interesting. Other age-dependent cellular changes reported in aging rodents and in larger animals include fibroblast
proliferation, collagen accumulation, and interstitial fibrosis in both the atria and the ventricles. Key structural changes linked to cardiac aging in humans and in animals are summarized in Table 1 and illustrated in Figure 1.

Our group has explored the link between biological age, measured as frailty, and age-dependent changes in the heart. We developed a method to quantify frailty with a “frailty index” based on the idea that health deficits accumulate with age. A frailty index score is obtained by counting the deficits in health in an individual and dividing by the total number of potential deficits to obtain a score between 0 (no deficits) and 1 (all possible deficits). Our work has shown that myocyte hypertrophy occurs predominantly in aged mice with high frailty scores. By contrast, mice of the same age with low frailty scores do not exhibit hypertrophy. Thus, some aspects of age-dependent remodelling might be more closely linked to biological age (frailty) than chronological age.

Impact of Age on Cardiac Function

Many structural changes associated with normal aging are maladaptive. For example, age-related increases in epicardial adipose tissue are associated with a higher prevalence of various CVDs, although whether pericardial adipose tissue increases with age is unclear. This could be important, because pericardial fat is a known risk factor for diseases such as atrial fibrillation, which is common in older adults. Calcification of the aortic valve leaflets impairs their movement, which can obstruct LV outflow and promote the development of heart failure, especially in older men. The concept that age adversely affects heart structure and predisposes elderly individuals to acquire heart disease has encouraged interest in the effects of age on electrical and contractile function of the heart.

Influence of age on pacemaker and cardiac conduction processes

Heart rate (HR) is not affected by age in supine men and women. There is also no difference in resting HRs between young adult and aged rodents of both sexes. However, HR increases less in older adults than in younger adults when they move from a supine to a seated position. This impaired ability to increase HR arises, in part, because of the age-associated decline in responsiveness to sympathetic stimulation, as discussed in the section The Impact of Age on Heart Function During Exercise. A decline in pacemaker cell number and reduced ion channel
expression in SAN cells may diminish automaticity and contribute to lower HRs in older adults.6,21 Age-related SAN dysfunction may help explain the development of bradyarrhythmias and symptoms that require pacemaker implantation in older adults.6,21 The conduction system changes characteristically with age. Age-related prolongation of the QRS complex, consistent with a slowing of conduction, is seen in humans and animals.7 Animal studies demonstrate that reduced cell-to-cell connections, mediated by lower expression of connexin-43, slow conduction in the aging heart.31 These age-dependent changes in conduction may promote dysrhythmias in older adults.

Age-dependent atrial remodelling

In young adults, early LV filling occurs rapidly so that very little filling is caused by atrial contraction later in diastole. By contrast, slow early LV filling is a characteristic feature of the aging heart, as discussed in more detail in the section Diastolic Dysfunction. Slow LV filling increases diastolic filling pressure, which results in atrial dilatation and hypertrophy.5 This enhances the force of atrial contraction and promotes late diastolic filling to compensate for reduced filling early in diastole.1 In consequence, the atria make a larger contribution to ventricular filling in older adults than in younger adults. Thus, attenuation of atrial contraction in diseases such as atrial fibrillation can markedly reduce diastolic volumes in older individuals.5 This reduces cardiac output, which predisposes older individuals toward the development of heart failure.

Dilatation is not the only change in aging atria. Along with the loss of SAN cells, there is a loss of atrial myocytes and increased interstitial fibrosis.5 Indeed, atrial fibrosis increases with age in both men and women.29,30 Atrial fibrosis also increases in older dogs, although whether this differs between the sexes is unclear.31 Mechanisms implicated in cardiac fibrosis include chronic systemic activation of the renin-angiotensin-aldosterone system, mitochondrial dysfunction, and generation of reactive oxygen species,14,52 as discussed in the section Cellular Mechanisms of Dysfunction in the Aging Heart.

Other studies have investigated age-dependent changes in atrial electrophysiology. Most studies have used atrial myocytes from patients with underlying CVD, and few have examined individuals older than 70 years of age.14 Thus, whether age influences the electrophysiological properties of atrial myocytes from healthy older humans is not clear. Studies in older animals have shown that right atrial myocytes are depolarized, with longer action potentials than those in younger animals.35 These changes in action potential configuration are associated with an increase in potassium currents, although calcium currents in these cells decline with age.35 Together, age-related changes in ion channels, along with atrial fibrosis and hypertrophy, provide an ideal substrate for the development of atrial fibrillation, which is common in older adults.37 There is evidence for a higher incidence of atrial fibrillation in men, although women often have worse outcomes, including stroke and systemic embolization.34 Interestingly, susceptibility to atrial fibrillation also increases with age in mice, at least in male mice.35 Whether age-dependent atrial remodelling differs between the sexes is not yet clear, and additional studies are warranted.

Age and sex affect resting systolic function

Traditionally, measures of systolic function, including stroke volume and ejection fraction, were said to be similar in young and older adults at rest.47 More recent evidence indicates that cardiac contractility is well preserved in women but actually declines in men after age 50 years.35 Interestingly, echocardiographic studies in animals support this view. Systolic function (stroke volume, ejection fraction) declines with age in male rodents but not in female rodents.44,50,54,55 Corresponding changes occur at the cellular level. There is some evidence from studies in both humans and animals that the number of ventricular myocytes declines with age in the male but not the female sex.4,22 Furthermore, our work in
rodents has shown that the ability of ventricular myocytes to contract declines with age in male rodents more than in female rodents. 24,25 We have also shown that reduced contractile function in cells from male rodents is caused by an age-dependent decline in peak calcium transients. 24,42,43 These findings are consistent with older men being more likely than older women to experience heart failure with reduced ejection fraction (HFrEF). 46

Frailty also appears to affect contractile function in older adults. We have found that cellular contractile depression occurs in mice with the highest frailty scores, whereas those with lower scores show little evidence of contractile dysfunction. 45 This is important because frailty is common in older patients with heart failure, who experience worse outcomes and higher mortality than do nonfrail patients of the same age. 36 That frailty predicts contractile dysfunction better than does chronological age suggests that frailty may predispose individuals toward the development of heart failure. 43

Diastolic dysfunction

Diastolic dysfunction, characterized by problems with relaxation, is a hallmark of cardiac aging. In young adult hearts, LV filling occurs early and rapidly as a consequence of ventricular relaxation. 44 By contrast, hearts from older individuals fill with blood more slowly. 45 Indeed, the rate of LV filling in the early diastolic phase declines with age by the sixth decade in both sexes. 46 This age-dependent slowing of relaxation in diastole may predispose the aging heart toward heart failure with preserved ejection fraction, commonly referred to as HFrEF. 37,39 HFrEF is characterized by increased wall thickness and diastolic dysfunction with little or no reduction in ejection fraction. 50,57 It is common in older adults, although there appear to be important male/female differences. 56,58,60 Risk factors for HFrEF also differ between the sexes, with factors such as myocardial ischemia being important in men and hypertension playing a major role in women. 58 The increase in diastolic dysfunction with age is significant, because population aging has led to a growing epidemic of HFrEF. Furthermore, although evidence-based treatments can improve prognosis in HFrEF, there are no current treatments for HFrEF.37,38

The increasing prevalence and lack of treatment options for HFrEF has promoted interest in the determinants of age-related diastolic dysfunction. Aging rodents of both sexes exhibit slowed relaxation and diastolic dysfunction. 48-50,54,55,57 This suggests that underlying mechanisms of potential relevance to humans can be investigated in animals. Several mechanisms have been implicated. For example, increased fibrosis is thought to increase ventricular stiffness. 13 This reduces ventricular compliance and impairs passive filling of the left ventricle. 37 The thicker less distensible LV walls seen in older humans and animal hearts also may contribute to the development of HFrEF. 5,10,19 In addition, increased myocyte stiffness, mediated by age-dependent changes in the sarcomeric protein titin, contribute to the increase in LV stiffness in HFrEF. 38 Changes in intracellular calcium homeostasis have also been implicated in the pathogenesis of HFrEF, as discussed in the section Cellular Mechanisms of Dysfunction in the Aging Heart.
effect on peak calcium transients, calcium currents, or contractions in cells from female rodents and actually enhances these responses in cells from aged sheep. This age-dependent decrease in peak calcium transients/contractions in myocytes from male animals but not female animals may help explain why systolic dysfunction and HFpEF are seen more in older men than in older women.

Altered calcium homeostasis also helps explain slowed relaxation and diastolic dysfunction in the aging heart. Prolongation of relaxation in the aging heart reflects a slower rate of decay of the calcium transient. This is clear in older diastole. There are additional age-related changes in contractile relaxation and compromises LV persistent activation of contractile elements. Studies have shown that activation of angiotensin II type 1 receptors on fibroblasts stimulates fibroblast proliferation, increases collagen synthesis, and augments the expression of extracellular matrix proteins. Angiotensin II is also thought to promote growth in adult cardiac myocytes by inducing the expression of growth factors such as transforming growth factor β. Chronic exposure to angiotensin II also damages the heart by increasing cellular and mitochondrial ROS, as discussed in the section Mitochondrial Dysfunction. These similarities between the angiotensin II—treated heart and the aging heart suggest that angiotensin II may play a role in cardiac aging. Indeed, evidence from rodent models has shown that cardiac angiotensin II levels increase with age, and this has been linked to hypertrophy, fibrosis, and diastolic dysfunction in the aging heart. Interestingly, the effects of angiotensin on the aging heart appear to differ between the sexes. For example, female mice with elevated intracardiac levels of angiotensin II exhibit age-dependent contractile depression, whereas male mice do not. These findings support the concept that the influence of age on the heart differs prominently between the sexes.

Mitochondrial dysfunction

The heart is rich in mitochondria that help provide the energy required for optimal myocardial function. Conversely, mitochondrial misregulation is a major source of ROS production, so high levels of these organelles in the heart increase its risk of oxidative damage. Indeed, ROS generation increases with age in both humans and animals. The increase in ROS in the aging heart is similar in the male and female sexes, at least in animal models. It is currently thought that the age-associated increase in mitochondrial ROS damages mitochondrial DNA, which disrupts mitochondrial function, further increasing ROS production and damaging mitochondrial DNA plus other macromolecules. This age-dependent increase in oxidative damage can help explain mitochondrial dysfunction in the aging heart.

The key role of ROS generation and mitochondrial dysfunction in cardiac aging is supported by experiments that target mitochondrial ROS. For example, overexpression of the ROS scavenger enzyme catalase attenuates the development of hypertrophy, fibrosis, and diastolic dysfunction in the aging mouse heart. By contrast, prematurely aging mice with a mutation in mitochondrial DNA polymerase exhibit marked cardiac hypertrophy and fibrosis as well as systolic and diastolic dysfunction. Together, these observations suggest that ROS generation and mitochondrial damage contribute to cardiac aging. Still, the role of ROS accumulation in aging is controversial because some studies suggest that intracellular ROS may also have beneficial effects in aging, so this remains an active area of research.

Understanding the aging context

Much of the research reviewed here has focused on a small number of mechanisms in the context of aging changes. Many studies have only used males of the species in the belief
(generally false)\textsuperscript{22} that the estrus cycle gives too great a degree of variability for valid conclusions about the impact of age. Ironically, much less attention has been paid to the well-recognized variability in degree of age-related changes in animals of the same age,\textsuperscript{73,74} which is the basis of frailty.\textsuperscript{75} For this reason, our group has developed frailty measures for use in mouse models,\textsuperscript{76} including 1 that is suitable for longitudinal study.\textsuperscript{44,76} Preclinical studies in animal models of frailty may help translate animal work into human treatments.

**Summary**

The incidence of CVD increases with age in both sexes, although men and women are predisposed toward different CVDs as they age.\textsuperscript{36,38} Male/female differences in coronary artery disease, including a higher risk of obstructive disease in men and more microvascular disease in women,\textsuperscript{77} clearly contribute to sex differences in CVD expression. In addition, as reviewed here, there are marked age-dependent changes in the structure and function of the heart that differ between the sexes. This cardiac remodelling occurs even in healthy older adults with no signs of overt CVD. Still, whether cardiac aging itself represents a disease is debated. Sir John Grimley Evans once said that “to draw a distinction between disease and normal aging is to attempt to separate the undefined from the definable.”\textsuperscript{78} More recently, Lakatta argued that cardiac aging is a disease,\textsuperscript{79} in part because many of its adverse effects can be modified by factors such as changes in diet and exercise. Although the relationship between cardiac aging and heart disease may be contested, there is little doubt that age-associated structural and functional changes in the heart have potentially important clinical consequences, as summarized in Table 1. Table 1 also indicates that many features of cardiac aging differ between the sexes, although more work in this area is clearly needed. There is emerging evidence that frailty may have a major impact on cardiac aging, an idea that is motivating additional research by our group. An improved understanding of the mechanisms involved in the effects of age and frailty on both male and female hearts may help explain why men and women are susceptible to different CVDs as they age and may help identify new treatments for these diseases in both sexes.

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