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Review

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

RÉSUMÉ

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 fibrillation 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.[1] Calcification of specific

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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 ß-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.

sur le cœur sont évidents au repos, mais plus encore à l'effort. Par ailleurs, des données montrent que le remodelage cardiaque s'effectue différemment en fonction du sexe. Par exemple, on sait désormais que le mécanisme d'apoptose entraîne une diminution du nombre de myocytes ventriculaires chez l'homme, mais pas chez la femme. Cela explique pourquoi les hommes sont plus susceptibles que les femmes de souffrir d'une insuffisance cardiaque avec réduction de la fraction d'éjection ventriculaire gauche. Des données probantes récentes, issues d'études précliniques, portent à croire que le remodelage cardiaque pathologique serait plus fonction de la fragilité de l'organisme que de l'âge chronologique de la personne. Parmi les mécanismes pathologiques impliqués dans le vieillissement cardiaque, on retrouve notamment les altérations du métabolisme calcique, l'activation excessive des systèmes ß-adrénergique et rénine-angiotensine ainsi que la dysfonction mitochondriale. Il faudra mener davantage de recherches sur le vieillissement cardiaque chez l'homme et la femme, car une meilleure compréhension des mécanismes sous-jacents permettrait sans doute de mieux adapter les stratégies de traitement des MCV.

regions, including the aortic valve leaflets, also occurs in older adults.[2] 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 CVD is present.[3] Left ventricular (LV) wall thickness increases in healthy older adults, whereas LV systolic and diastolic volumes decline with age in both sexes.[4] Whether LV mass is affected by age is controversial,[4,5] 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.[6] 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.[7,8] The loss of myocytes may result from apoptosis, necrosis, or autophagy (or a combination),[9-11] although limited regenerative ability of stem cells also may contribute.[12] 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.[7,8] 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.[13] The accumulation of collagen leads to interstitial fibrosis in the atria, SANs, and ventricles of older adults.[6,14] 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,[15] comparable to that in 85-year-old humans,[16] 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.[17,18] There is also evidence for atrial hypertrophy and dilatation in older rodents, and LV wall thickness increases with age in older rats and mice.[10,19,20]

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.[21] 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.[22] 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.[23] 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.[23-26] 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

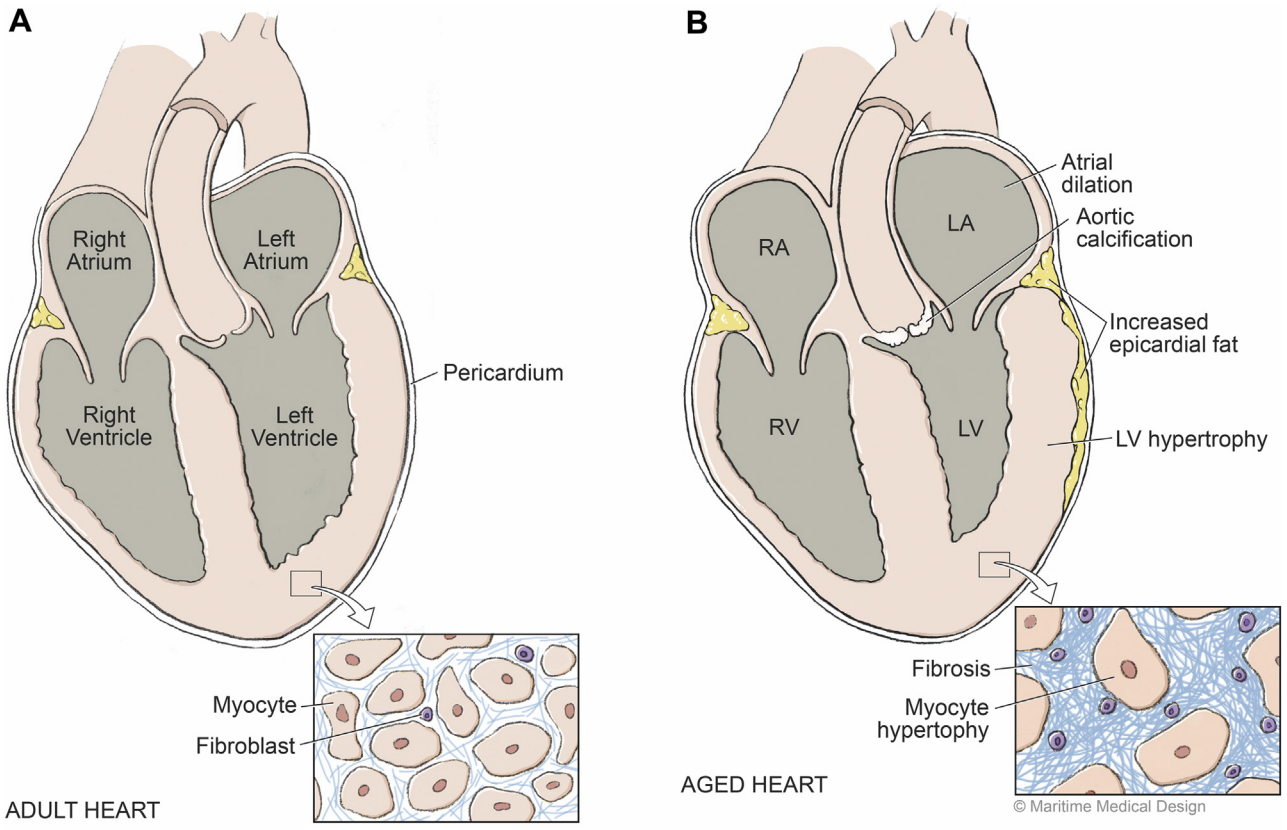

Figure 1. Major age-dependent changes in the structure of the heart at the macroscopic and microscopic levels. (**A**) Young adult heart. (**B**) Aged heart. Compared with the younger adult heart, the aged heart exhibits gross structural changes, including epicardial fat deposition, calcification of the aortic valve, atrial hypertrophy and dilatation, as well as hypertrophy of the left ventricle. Changes at the cellular level include the loss of ventricular myocytes and hypertrophy of the remaining cells. There is also an increase in the number of fibroblasts with age and a marked increase in fibrosis. Some of these age-dependent changes may be modified by factors such as sex and frailty, as discussed in the text. Illustration by Monique Guilderson. Reproduced with permission of Maritime Medical Design and Monique Guilderson.

proliferation, collagen accumulation, and interstitial fibrosis in both the atria and the ventricles.[13,19,27] 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.[43,44] 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.[43] By contrast, mice of the same age with low frailty scores do not exhibit hypertrophy.[43] 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,[45] 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.[46] Calcification of the aortic valve leaflets impairs their movement, which can obstruct LV outflow and promote the development of heart failure,[2] especially in older men.[28] 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.[47] There is also no difference in resting HRs between young adult and aged rodents of both sexes.[48-50] However, HR increases less in older adults than in younger adults when they move from a supine to a seated position.[47] This impaired ability to increase HR arises, in part, because of the age-associated decline in responsiveness to sympathetic stimulation,[41] as discussed in the section *The Impact of Age on Heart Function During Exercise*. A decline in pacemaker cell number and reduced ion channel

Table 1. Clinical consequences of cardiac aging

Age-related change	Consequences	Sex difference
Aortic valve calcification[2,18]	Promotes heart failure[2]	More common in men[28]
Loss of SAN cells[6]	Lower HR[6,21]	Unclear
↓ Expression SAN channels[21]	Promotes bradycardias[6,21]	
↑ Late diastolic filling[4]	↑ Atrial contraction[4]	Unclear
↓ Early diastolic filling[5]	Atrial hypertrophy[5]	
Atrial hypertrophy[5]	Increases susceptibility to atrial fibrillation[32,33]	More prevalent in men[34]
Atrial fibrosis[6,29-31]		Worse outcomes in women[34]
Electrical remodelling of atria[35]		
Fewer ventricular myocytes[7,8,22]	Promotes heart failure, especially HFrEF[36]	Cell loss and hypertrophy may be worse in men[7,8,22]
Myocyte hypertrophy[7,8,22]		Systolic function worse in men[36]
↓ Myocyte contraction[23,24]		
↓ Calcium transient[23,24]		
↓ Systolic function[36]		
↑ LV wall thickness[4,10,19]	Promotes diastolic dysfunction[10,37]	More prevalent in women[36,38]
↑ LV fibrosis and stiffness[6,13,14,20]	Predisposes toward HFpEF[37,39]	Worse outcomes in men[40]
Slowed calcium removal[23]		
↑ Diastolic calcium[23]		
Slow passive LV filling[10,37]		
↓ Sensitivity to β-adrenergic stimulation[41]	Impairs ability to ↑ HR and force in exercise	May be more pronounced in men[42]

HR, heart rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; SAN, sinoatrial node.

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 cardiac 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.[6,51] Animal studies demonstrate that reduced cell-to-cell connections, mediated by lower expression of connexin-43, slow conduction in the aging heart.[51] 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.[4] 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.[6] 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.[35] 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.[32] 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.[33] 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.[53] 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.[48-50,54,55]

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.[7,8,22] 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.[24,25] These findings are consistent with older men being more likely than older women to experience heart failure with reduced ejection fraction (HFrEF).[36]

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.[43] 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.[56] 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.[5,47] By contrast, hearts from older individuals fill with blood more slowly.[5,47] Indeed, the rate of LV filling in the early diastolic phase declines with age by the sixth decade in both sexes.[3] This age-dependent slowing of relaxation in diastole may predispose the aging heart toward heart failure with preserved ejection fraction, commonly referred to as HFpEF.[37,39] HFpEF is characterized by increased wall thickness and diastolic dysfunction with little or no reduction in ejection fraction.[50,53] It is common in older adults, although there appear to be important male/female differences.[36,38,40] Risk factors for HFpEF also differ between the sexes, with factors such as myocardial ischemia being important in men and hypertension playing a major role in women.[38] The increase in diastolic dysfunction with age is significant, because population aging has led to a growing epidemic of HFpEF. Furthermore, although evidence-based treatments can improve prognosis in HFrEF, there are no current treatments for HFpEF.[37,38]

The increasing prevalence and lack of treatment options for HFpEF 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 HFpEF.[4,10,19] In addition, increased myocyte stiffness, mediated by age-dependent changes in the sarcomeric protein titin, contribute to the increase in LV stiffness in HFpEF.[58] Changes in intracellular calcium homeostasis have also been implicated in the pathogenesis of HFpEF, as discussed in the section *Cellular Mechanisms of Dysfunction in the Aging Heart*.

The impact of age on cardiac function during exercise

The effects of cardiac aging are seen more clearly during exercise when the heart must respond to stress. Although resting HRs are not affected by age, the maximum HR achieved during exercise declines with age in both sexes.[59] Reduced sensitivity of the myocardium to sympathetic stimulation is implicated. Normally, activation of the sympathetic nervous system during exercise releases catecholamines (eg, noradrenaline, adrenaline) that activate β-adrenergic receptors in the heart to increase the rate and force of contraction. However, the evidence that the heart's responsiveness to β-adrenergic stimulation declines with age in humans and animals is strong,[41,42,60-62] as discussed in the section *Intracellular Calcium Homeostasis*. Interestingly, 1 study in nonhuman primates found that in vivo responses to β-adrenergic receptor stimulation declined with age in the male but not the female sex.[42] Still, whether responsiveness to catecholamines differs between the sexes is unclear, because most clinical/preclinical studies have either focused on older male animals or have not investigated sex differences.

Because HR is a key determinant of cardiac output, a lower maximum HR is thought to impair the ability of the aging heart to augment cardiac output during exercise.[5] The age-dependent decrease in sensitivity to β-adrenergic stimulation also directly limits the increase in contractile force in response to exercise in older adults.[41,42,60-62] These changes appear mitigated, in part, by an increase in LV end-diastolic volume during exercise in older adults.[5] This produces more blood in the ventricle at the end of diastole, which through the Frank-Starling mechanism increases stretch on the heart and the strength of contraction. Greater reliance on the Frank-Starling mechanism may at least partially compensate for the lower HR and reduced contractility of the aging heart during exercise.[5] The major structural and functional changes associated with cardiac aging, along with potential clinical consequences and important sex differences, are summarized in Table 1.

Cellular Mechanisms of Dysfunction in the Aging Heart

Animal models have yielded evidence for a variety of molecular mechanisms that contribute to structural and functional remodelling of the aging heart. A full consideration of the mechanisms implicated in cardiac aging is beyond this review's remit. We focus on altered calcium homeostasis, chronic systemic activation of the β-adrenergic and renin-angiotensin pathways, and mitochondrial dysfunction as likely mechanisms in key aspects of cardiac aging.

Intracellular calcium homeostasis

Cardiac contraction and relaxation reflect the rise and fall of intracellular calcium levels in individual cardiac myocytes. Age-dependent changes in the regulation of intracellular calcium affect the ability of the heart to contract.[23] For example, smaller calcium transients are responsible for the smaller contractions observed in ventricular myocytes from aged male rodents compared with younger animals.[24,25] Smaller calcium transients are thought to arise, in part, from a reduction in peak calcium currents, leading to less calcium influx in myocytes from aged male rodents.[23] By contrast, age has little

effect on peak calcium transients, calcium currents, or contractions in cells from female rodents and actually enhances these responses in cells from aged sheep.[23,26] The age-dependent decrease in peak calcium transients/contractions in myocytes from male animals but not female animals may help explain why systolic dysfunction and HFrEF are seen more in older men than in older women.[36]

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.[23] This is clear in older male animals but less so in older female animals, although few studies have used female animals.[23] Slower calcium transient decay arises from reduced calcium uptake into stores in the sarcoplasmic reticulum (SR), resulting from reduced expression and activity of the SR calcium−adenosine triphosphatase pump.[23] Prolonged availability of internal calcium causes persistent activation of contractile filaments, which delays active ventricular relaxation and compromises LV filling in early diastole.[10,37] There are additional age-related changes in contractile proteins in both sexes.[23] There is a shift from the fast α-myosin heavy chain isoform to the slower β-isoform with age in hearts from both sexes, which can slow relaxation.[23] These changes help explain the increase in HFpEF in older adults.[37,39] Still, why HFpEF occurs more commonly in women, whereas outcomes are worse in men, obliges further investigations.

Chronic activation of the β-adrenergic and renin-angiotensin pathways

Normally, activation of cardiac β-adrenergic receptors increases HR and contractile force, but there is strong evidence that myocardial responsiveness to β-adrenergic stimulation declines with age.[41] This age-related decline in sensitivity to catecholamine stimulation has been attributed to high levels of circulating catecholamines, which lead to chronic activation of the β-adrenergic pathway in humans and animals.[41,42,63] Chronic activation of this pathway arises from reduced plasma clearance of noradrenaline and increased catecholamine spillover into circulation from organs such as the heart.[41] Chronic activation of the β-adrenergic pathway has been implicated in several aspects of cardiac aging. For example, chronic β-adrenergic stimulation can damage the heart by increasing the production of mitochondrial reactive oxygen species (ROS),[10] as discussed in the section *Mitochondrial Dysfunction*. It also can desensitize elements of the β-adrenergic signalling cascade and limit the increased HR response seen with changing position or with exercise.[41,47] Desensitization of the β-adrenergic pathway in aging also limits the increase in force normally seen in response to exercise.[41] The underlying mechanisms have not been fully elucidated, but there is evidence that fewer β-adrenergic receptors, less cyclic adenosine monophosphate production or desensitization of other components of the β-adrenergic signalling pathway (or a combination) play a role.[41,42,60-62] Animal studies suggest that circulating catecholamine levels increase with age to a lesser extent in female animals than in male animals.[42] Although this has not yet been observed in humans,[63] few studies have directly compared older men and women. Additional studies in humans and animal models could clarify this issue.

Chronic activation of the renin-angiotensin system also is thought to play a role in cardiac aging. In younger animals, chronic infusion of angiotensin II causes cardiac hypertrophy, fibrosis, and slowed relaxation,[64] a phenotype that resembles cardiac aging. 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.[64] 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.[64] Chronic exposure to angiotensin II also damages the heart by increasing cellular and mitochondrial ROS,[10] 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.[65] 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.[66] 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 respiration is a major source of ROS production, so high levels of these organelles in the heart increase its risk of oxidative damage.[10] Indeed, ROS generation increases with age in both humans and animals.[67,68] The increase in ROS in the aging heart is similar in the male and female sexes, at least in animal models.[69] 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.[70] This age-dependent increase in oxidative damage can help explain mitochondrial dysfunction in the aging heart.[70]

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.[65] 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.[71] 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,[68] 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)[72] 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,[73,74] which is the basis of frailty.[75] For this reason, our group has developed frailty measures for use in mouse models,[43] including 1 that is suitable for longitudinal study.[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.[36,38] Male/female differences in coronary artery disease, including a higher risk of obstructive disease in men and more microvascular disease in women,[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 indefinable."[78] More recently, Lakatta argued that cardiac aging is a disease,[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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References

1. Silaghi A, Piercecchi-Marti M-D, Grino M, et al. Epicardial adipose tissue extent: relationship with age, body fat distribution, and coronaropathy. Obesity 2008;16:2424-30.
2. New SE, Aikawa E. Cardiovascular calcification: an inflammatory disease. Circ J 2011;75:1305-13.
3. Boyd AC, Schiller NB, Leung D, Ross DL, Thomas L. Atrial dilation and altered function are mediated by age and diastolic function but not before the eighth decade. JACC Cardiovasc Imaging 2011;4:234-42.
4. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin 2012;8:143-64.
5. Fleg JL, Strait J. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. Heart Fail Rev 2012;17:545-54.
6. Mirza M, Strunets A, Shen WK, et al. Mechanisms of arrhythmias and conduction disorders in older adults. Clin Geriatr Med 2012;28:555-73.
7. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circ Res 1991;68:1560-8.
8. Olivetti G, Giordano G, Corradi D, et al. Gender differences and aging: effects on the human heart. J Am Coll Cardiol 1995;26:1068-79.
9. Sheydina A, Riordon DR, Boheler KR. Molecular mechanisms of cardiomyocyte aging. Clin Sci (Lond) 2011;121:315-29.
10. Dai DF, Chen T, Johnson SC, et al. Cardiac aging: from molecular mechanisms to significance in human health and disease. Antioxid Redox Signal 2012;16:1492-526.
11. Leon LJ, Gustafsson ÅB. Staying young at heart: autophagy and adaptation to cardiac aging. J Mol Cell Cardiol 2016;95:78-85.
12. Hariharan N, Sussman MA. Cardiac aging—getting to the stem of the problem. J Mol Cell Cardiol 2015;83:32-6.
13. Horn MA, Trafford AW. Aging and the cardiac collagen matrix: novel mediators of fibrotic remodeling. J Mol Cell Cardiol 2016;93:175-85.
14. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac fibrosis in patients with atrial fibrillation: mechanisms and clinical implications. J Am Coll Cardiol 2015;66:943-59.
15. Turturro A, Witt WW, Lewis S, et al. Growth curves and survival characteristics of the animals used in the Biomarkers of Aging Program. J Gerontol A Biol Sci Med Sci 1999;54:B492-501.
16. Grundy EMD. The epidemiology of aging. In: Tallis R, Fillit H, eds. Brocklehurst's Textbook of Geriatric Medicine and Gerontology. 6th ed. London: Churchill Livingstone, 2003:4-20.
17. Swifka J, Weiss J, Addicks K, Eckel J, Rösen P. Epicardial fat from guinea pig: a model to study the paracrine network of interactions between epicardial fat and myocardium? Cardiovasc Drugs Ther 2008;22:107-14.
18. Roosens B, Bala G, Droogmans S, et al. Occurrence of cardiovascular calcifications in normal, aging rats. Exp Gerontol 2012;47:614-9.
19. Lindsey ML, Goshorn DK, Squires CE, et al. Age-dependent changes in myocardial matrix metalloproteinase/tissue inhibitor of metalloproteinase profiles and fibroblast function. Cardiovasc Res 2005;66:410-9.
20. Lau DH, Shipp NJ, Kelly DJ, et al. Atrial arrhythmia in ageing spontaneously hypertensive rats: unraveling the substrate in hypertension and ageing. PLoS One 2013;8:e72416.
21. Tellez JO, Mczewski M, Yanni J, et al. Ageing-dependent remodelling of ion channel and Ca2+ clock genes underlying sino-atrial node pacemaking. Exp Physiol 2011;96:1163-78.
22. Zhang XP, Vatner SF, Shen YT, et al. Increased apoptosis and myocyte enlargement with decreased cardiac mass; distinctive features of the aging male, but not female, monkey heart. J Mol Cell Cardiol 2007;43:487-91.

23. Feridooni HA, Dibb KM, Howlett SE. How cardiomyocyte excitation, calcium release and contraction become altered with age. J Mol Cell Cardiol 2015;83:62-72.

24. Howlett SE. Age-associated changes in excitation-contraction coupling are more prominent in ventricular myocytes from male rats than in myocytes from female rats. Am J Physiol Heart Circ Physiol 2010;298: H659-70.

25. Grandy SA, Howlett SE. Cardiac excitation-contraction coupling is altered in myocytes from aged male mice but not in cells from aged female mice. Am J Physiol Heart Circ Physiol 2006;291:H2362-70.

26. Dibb KM, Rueckschloss U, Eisner DA, Isenberg G, Trafford AW. Mechanisms underlying enhanced cardiac excitation contraction coupling observed in the senescent sheep myocardium. J Mol Cell Cardiol 2004;37:1171-81.

27. Horn MA, Graham HK, Richards MA, et al. Age-related divergent remodeling of the cardiac extracellular matrix in heart failure: collagen accumulation in the young and loss in the aged. J Mol Cell Cardiol 2012;53:82-90.

28. Milin AC, Vorobiof G, Aksoy O, Ardehali R. Insights into aortic sclerosis and its relationship with coronary artery disease. J Am Heart Assoc 2014;3:e001111.

29. Goette A, Juenemann G, Peters B, et al. Determinants and consequences of atrial fibrosis in patients undergoing open heart surgery. Cardiovasc Res 2002;54:390-6.

30. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol 2015;65:2239-51.

31. Anyukhovsky EP, Sosunov EA, Plotnikov A, et al. Cellular electrophysiologic properties of old canine atria provide a substrate for arrhythmogenesis. Cardiovasc Res 2002;54:462-9.

32. Brandenburg S, Arakel EC, Schwappach B, Lehnart SE. The molecular and functional identities of atrial cardiomyocytes in health and disease. Biochim Biophys Acta 2016;1863:1882-93.

33. Guo X, Yuan S, Liu Z, Fang Q. Oxidation- and CaMKII-mediated sarcoplasmic reticulum Ca^{2+} leak triggers atrial fibrillation in aging. J Cardiovasc Electrophysiol 2014;25:645-52.

34. Pancholy SB, Sharma PS, Pancholy DS, et al. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. Am J Cardiol 2014;113:485-90.

35. Dun W, Boyden PA. Aged atria: electrical remodeling conducive to atrial fibrillation. J Interv Card Electrophysiol 2009;25:9-18.

36. Dunlay SM, Roger VL. Gender differences in the pathophysiology, clinical presentation, and outcomes of ischemic heart failure. Curr Heart Fail Rep 2012;9:267-76.

37. Loffredo FS, Nikolova AP, Pancoast JR, et al. Heart failure with preserved ejection fraction: molecular pathways of the aging myocardium. Circ Res 2014;115:97-107.

38. Greiten LE, Holditch SJ, Arunachalam SP, Miller VM. Should there be sex-specific criteria for the diagnosis and treatment of heart failure? J Cardiovasc Transl Res 2014;7:139-55.

39. Kaila K, Haykowsky MJ, Thompson RB, et al. Heart failure with preserved ejection fraction in the elderly: scope of the problem. Heart Fail Rev 2012;17:555-62.

40. Lam CS, Carson PE, Anand IS, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2012;5:571-8.

41. Ferrara N, Komici K, Corbi G, et al. β-adrenergic receptor responsiveness in aging heart and clinical implications. Front Physiol 2014;4:396.

42. Takagi G, Asai K, Vatner SF, et al. Gender differences on the effects of aging on cardiac and peripheral adrenergic stimulation in old conscious monkeys. Am J Physiol Heart Circ Physiol 2003;285:H527-34.

43. Parks RJ, Fares E, Macdonald JK, et al. A procedure for creating a frailty index based on deficit accumulation in aging mice. J Gerontol A Biol Sci Med Sci 2012;67:217-27.

44. Whitehead JC, Hildebrand BA, Sun M, et al. A clinical frailty index in aging mice: comparisons with frailty index data in humans. J Gerontol A Biol Sci Med Sci 2014;69:621-32.

45. Sacks HS, Fain JN. Human epicardial fat: what is new and what is missing? Clin Exp Pharmacol Physiol 2011;38:879-87.

46. Al-Rawahi M, Proietti R, Thanassoulis G. Pericardial fat and atrial fibrillation: epidemiology, mechanisms and interventions. Int J Cardiol 2015;195:98-103.

47. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part II: the aging heart in health: links to heart disease. Circulation 2003;107:346-54.

48. Fannin J, Rice KM, Thulluri S, et al. Age-associated alterations of cardiac structure and function in the female F344xBN rat heart. Age (Dordr) 2014;36:9684.

49. Medrano G, Hermosillo-Rodriguez J, Pham T, et al. Left atrial volume and pulmonary artery diameter are noninvasive measures of age-related diastolic dysfunction in mice [e-pub ahead of print]. J Gerontol A Biol Sci Med Sci 2015, accessed November 24, 2015.

50. Koch SE, Haworth KJ, Robbins N, et al. Age- and gender-related changes in ventricular performance in wild-type FVB/N mice as evaluated by conventional and vector velocity echocardiography imaging: a retrospective study. Ultrasound Med Biol 2013;39:2034-43.

51. Bonda TA, Szynaka B, Sokołowska M, et al. Remodeling of the intercalated disc related to aging in the mouse heart [e-pub ahead of print]. J Cardiol http://dx.doi.org/10.1016/j.jjcc.2015.10.001, accessed December 14, 2015.

52. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008;51:802-9.

53. Claessens TE, Rietzschel ER, De Buyzere ML, et al. Noninvasive assessment of left ventricular and myocardial contractility in middle-aged men and women: disparate evolution above the age of 50? Am J Physiol Heart Circ Physiol 2007;292:H856-65.

54. Shinmura K, Tamaki K, Sano M, et al. Impact of long-term caloric restriction on cardiac senescence: caloric restriction ameliorates cardiac diastolic dysfunction associated with aging. J Mol Cell Cardiol 2011;50: 117-27.

55. Dai DF, Karunadharma PP, Chiao YA, et al. Altered proteome turnover and remodeling by short-term caloric restriction or rapamycin rejuvenate the aging heart. Aging Cell 2014;13:529-39.

56. Uchmanowicz I, Loboz-Rudnicka M, Szelag P, Jankowska-Polanska B, Loboz-Grudzien K. Frailty in heart failure. Curr Heart Fail Rep 2014;11: 266-73.

57. Barger JL, Kayo T, Vann JM, et al. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. PLoS One 2008;3:e2264.

58. Hamdani N, Bishu KG, von Frieling-Salewsky M, Redfield MM, Linke WA. Deranged myofilament phosphorylation and function in experimental heart failure with preserved ejection fraction. Cardiovasc Res 2013;97:464-71.

59. Nes BM, Janszky I, Wisløff U, Støylen A, Karlsen T. Age-predicted maximal heart rate in healthy subjects: The HUNT fitness study. Scand J Med Sci Sports 2013;23:697-704.

60. Farrell SR, Howlett SE. The age-related decrease in catecholamine sensitivity is mediated by ß1-adrenergic receptors linked to a decrease in adenylate cyclase activity in ventricular myocytes from male Fischer 344 rats. Mech Ageing Dev 2008;129:735-44.

61. Brodde OE, Leineweber K. Autonomic receptor systems in the failing and aging human heart: similarities and differences. Eur J Pharmacol 2004;500:167-76.

62. White M, Roden R, Minobe W, et al. Age-related changes in beta-adrenergic neuroeffector systems in the human heart. Circulation 1994;90:1225-38.

63. Blandini F, Martignoni E, Melzi d'Eril GV, et al. Free plasma catecholamine levels in healthy subjects: a basal and dynamic study. The influence of age. Scand J Clin Lab Invest 1992;52:9-17.

64. Rosenkranz S. TGF-β1 and angiotensin networking in cardiac remodeling. Cardiovasc Res 2004;63:423-32.

65. Dai DF, Santana LF, Vermulst M, et al. Overexpression of catalase targeted to mitochondria attenuated murine cardiac aging. Circulation 2009;199:2789-97.

66. Mellor KM, Curl CL, Chandramouli C, et al. Ageing-related cardiomyocyte functional decline is sex and angiotensin II dependent. Age (Dordr) 2014;36:9630.

67. Judge S, Jang YM, Smith A, Hagen T, Leeuwenburgh C. Age-associated increases in oxidative stress and antioxidant enzyme activities in cardiac interfibrillar mitochondria: implications for the mitochondrial theory of aging. FASEB J 2005;19:419-21.

68. Payne BA, Chinnery PF. Mitochondrial dysfunction in aging: much progress but many unresolved questions. Biochim Biophys Acta 2015;1847:1347-53.

69. Sanz A, Hiona A, Kujoth GC, et al. Evaluation of sex differences on mitochondrial bioenergetics and apoptosis in mice. Exp Gerontol 2007;42:173-82.

70. Biala AK, Dhingra R, Kirshenbaum LA. Mitochondrial dynamics: orchestrating the journey to advanced age. J Mol Cell Cardiol 2015;83:37-43.

71. Dai DF, Chen T, Wanagat J, et al. Age-dependent cardiomyopathy in mitochondrial mutator mice is attenuated by overexpression of catalase targeted to mitochondria. Aging Cell 2010;9:536-44.

72. MacDonald JK, Pyle WG, Reitz CJ, Howlett SE. Cardiac contraction, calcium transients, and myofilament calcium sensitivity fluctuate with the estrous cycle in young adult female mice. Am J Physiol Heart Circ Physiol 2014;306:H938-53.

73. Fontana L, Kennedy BK, Longo VD, Seals D, Melov S. Medical research: treat ageing. Nature 2014;511:405-7.

74. Howlett SE, Rockwood K. Ageing: develop models of frailty. Nature 2014;512:253.

75. Howlett SE, Rockwood K. New horizons in frailty: ageing and the deficit-scaling problem. Age Ageing 2013;42:416-23.

76. Feridooni HA, Sun MH, Rockwood K, Howlett SE. Reliability of a frailty index based on the clinical assessment of health deficits in male C57BL/6J mice. J Gerontol A Biol Sci Med Sci 2015;70:686-93.

77. Gulati M, Shaw LJ, Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. Clin Cardiol 2012;35:141-8.

78. Evans JG. Ageing and disease. In: Evered D, Whalen J, eds. Research and the Aging Population. Ciba Foundation Symposium No 134. Chichester: John Wiley & Sons, 1988:38-57.

79. Lakatta EG. So! What's aging? Is cardiovascular aging a disease? J Mol Cell Cardiol 2015;83:1-13.